Improved survival for dose-intensive chemotherapy in primary mediastinal B-cell lymphoma: a systematic review and meta-analysis of 4,068 patients

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Abstract

Primary mediastinal B-cell lymphoma (PMBCL) is a distinct clinicopathologic entity. Currently, there is a paucity of randomized prospective data to inform on optimal front-line chemoimmunotherapy (CIT) and use of consolidative mediastinal radiation (RT). To assess if distinct CIT approaches are associated with disparate survival outcomes, we performed a systematic review and meta-analysis comparing dose-intensive (DI-CIT) *versus* standard CIT for the front-line treatment of PMBCL. Standard approach (S-CIT) was defined as R-CHOP-21/CHOP-21, with or without RT. DI-CIT were defined as regimens with increased frequency, dose, and/or number of systemic agents. We reviewed data on 4,068 patients (2,517 DI-CIT; 1,551 S-CIT) with a new diagnosis of PMBCL. Overall survival for DI-CIT patients was 88% (95% CI: 85-90) compared to 80% for the S-CIT cohort (95% CI: 74-85). Meta-regression revealed an 8% overall survival (OS) benefit for the DI-CIT group (P<0.01). Survival benefit was maintained when analyzing rituximab only regimens; OS was 91% (95% CI: 89-93) for the rituximab-DI-CIT arm compared to 86% (95% CI: 82-89) for the R-CHOP-21 arm (P=0.03). Importantly, 55% (95% CI: 43-65) of the S-CIT group received RT compared to 22% (95% CI: 15-31) of DI-CIT patients (meta-regression P<0.01). To our knowledge, this is the largest meta-analysis reporting efficacy outcomes for the front-line treatment of PMBCL. DI-CIT demonstrates a survival benefit, with significantly less radiation exposure, curtailing long-term toxicities associated with radiotherapy. As we await results of randomized prospective trials, our study supports the use of dose-intensive chemoimmunotherapy for the treatment of PMBCL.

Introduction

Primary mediastinal B-cell lymphoma (PMBCL) is recognized as a distinct diagnostic entity based on unique clinical and biological features.[1] It has significant overlap with classical Hodgkin lymphoma (cHL) as both diseases are putatively derived from a thymic B cell. PMBCL predominantly affects adolescents and young adults (AYA), with a predilection for females, and fortunately is highly curable with modern therapeutic approaches. However, based on its localization to the mediastinum, consolidation radiation therapy has historically been a critical component of treatment and continues to be used in a high proportion of patients.

The use of mediastinal radiation in this predominantly female AYA population is problematic given its well-recognized association with an increased risk of secondary malignancy, particularly breast cancer.[2] Curative strategies that obviate the need for radiation in PMBCL are, therefore, needed and the question of which strategies may be able to reliably omit RT is under investigation. To this point, retrospective studies in PMBCL demonstrate improved outcomes for dose-intensive chemoimmunotherapeutic approaches compared to R-CHOP-21.[3] Improved sensitivity of PMBCL to higher intensity therapeutics could potentially be explained by its young age distribution and/or tumor biology that closely resembles cHL, a disease known to benefit

from increased therapeutic intensity.[4] These hypothetical concepts have led to the investigation of dose-intensive chemoimmunotherapy (DI-CIT) for PMBCL, but currently there is a paucity of prospective randomized trials showing superiority of these treatment regimens compared to R-CHOP-21.[5] Thus, our study goal was to analyze all published first-line treatment data for PMBCL with either DI-CIT or standard approach chemoimmunotherapy (S-CIT), to evaluate differences in survival outcomes and reliance on mediastinal radiation.

Methods

We performed a comprehensive systematic review on the front-line treatment of PMBCL. Studies included in our meta-analysis were prospective or retrospective published datasets that reported treatment outcomes (progression-free survival, PFS; overall survival, OS) for specific CIT regimens for children and adults diagnosed with PMBCL. Standard chemoimmunotherapy (S-CIT) was defined as R-CHOP-21 or CHOP-21, with or without RT. DI-CIT approaches were defined as regimens that increase the frequency, dose or number of systemic agents in comparison to R-CHOP-21. Case reports, small case series (<5 PMBCL patients) and unpublished conference abstracts were excluded.

We searched MEDLINE, Embase, and Cochrane CENTRAL via Ovid and Web of Science for all published literature on this topic on February 8, 2022. Please refer to the *Online Supplementary Appendix* for complete search strategies. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline and the PRISMA extension statement.[6] Two independent authors screened all studies to compile a final list of included publications, from which data were extracted. Patient number, trial type, treatment, consolidative mediastinal RT, PFS, and OS data were collected from each study and divided according to individual CIT regimens for comparison. The primary outcome of our study was to assess OS for DI-CIT compared to S-CIT. Key secondary outcomes included comparing these two treatment cohort's PFS and use of consolidative mediastinal radiation. We also analyzed all endpoints for cohorts of patients treated with dose adjusted-EPOCH-R (da-EPOCH-R) compared to R-CHOP-21 and rituximab-DI-CIT compared to R-CHOP-21 (R-S-CIT).

Individual patient demographic and clinical characteristics were collected from each publication, then grouped for studies that reported characteristics for specific DI-CIT and S-CIT regimens. Data for pediatric-only studies are reported separately as reported clinical characteristics differed. Clinical characteristics that were not reported for the subpopulation of PMBCL within the published series could not be evaluated in this analysis.

Selected characteristics of the included studies were summarized as percentages. The significance of the difference in means or proportions between two groups was evaluated using the *t* test or χ^2 test. Meta-analysis was conducted separately for the selected outcomes of the study. Heterogeneity of proportions/risks across studies was tested using Cochran's Q-statistic. The I^2-statistic was also used as an indicator of the percentage of variation among the studies due to true heterogeneity rather than chance, with 25% indicating low heterogeneity, 50% moderate heterogeneity, and 75% high heterogeneity.[7] The fixed effect or random effects approach was followed using the inverse variance method depending on whether the study heterogeneity hypothesis was significant or not, and a large or small value of the I^2-statistic was obtained. For the random effects approach, heterogeneity variance was estimated using the DerSimonian-Laird approach.[8] Meta-regression analysis (*Online Supplementary Table S1*) was used to evaluate the significance of the difference in outcome (proportion) between DI-CIT and S-CIT (as well as for subgroup analysis), adjusted for years of follow-up. The meta-analysis was conducted using the METAPROP and METAREG functions in the package META in R for Windows.[9]

Results

Overall, the literature search identified 2,112 studies (Figure 1), which resulted in the inclusion of 52 publications:[3,10-60] 11 prospective and 41 retrospective studies. This identified 4,068 PMBCL adult and pediatric patients who were treated with first-line dose-intensive (n=2,517) and standard (n=1,551) chemoimmunotherapy.

Reported demographic and clinical characteristics varied in each publication; Table 1 summarizes the most commonly reported patients' characteristics. In the DI-CIT cohort (24 evaluable studies), median age of patients was 32.8 years (60.5% female). Most patients were classified as stage I or II disease (67.7%) with a majority reported to have a bulky mediastinal mass (>10 cm or 1/3 of the thoracic diameter; 72.7%). Lactate dehydrogenase (LDH) was elevated in 77.7% and 35.6% had extranodal involvement. In the S-CIT cohort (19 evaluable studies), median age was 33.8 years (56.3% female). Again, the majority of patients had stage I/II disease (70.7%) with bulky mediastinal involvement (62.7%). LDH was elevated in 71.5% of this cohort, with 35.3% of patients reported to have extranodal involvement. The test for difference in means (or proportions) of selected characteristics between D-CIT and S-CIT was significant for the median age, gender, B symptoms, bulky disease, and elevated LDH. Clinical characteristics reported in publications that did not report separate patients' characteristics for different treatment regimens, as well as pediatric only studies are reported in *Online Supplementary Tables S2* and *S3*. Table 2 summarizes the CIT regimens that were

included. In the DI-CIT cohort, the majority of patients received da-EPOCH-R (n=670), VACOP/MACOP-B +/- rituximab (n=458), and "2nd/3rd generation chemotherapy" (VACOP/MACOP-B, ProMACE, CytaBOM, n=375). There were 329 pediatric patients included in the DI-CIT cohort who received a variety of intensive pediatric regimens (IPR). In the S-CIT cohort, 1,095 patients received R-CHOP-21 and 456 were treated with CHOP-21. In the DI-CIT group, 60.5%

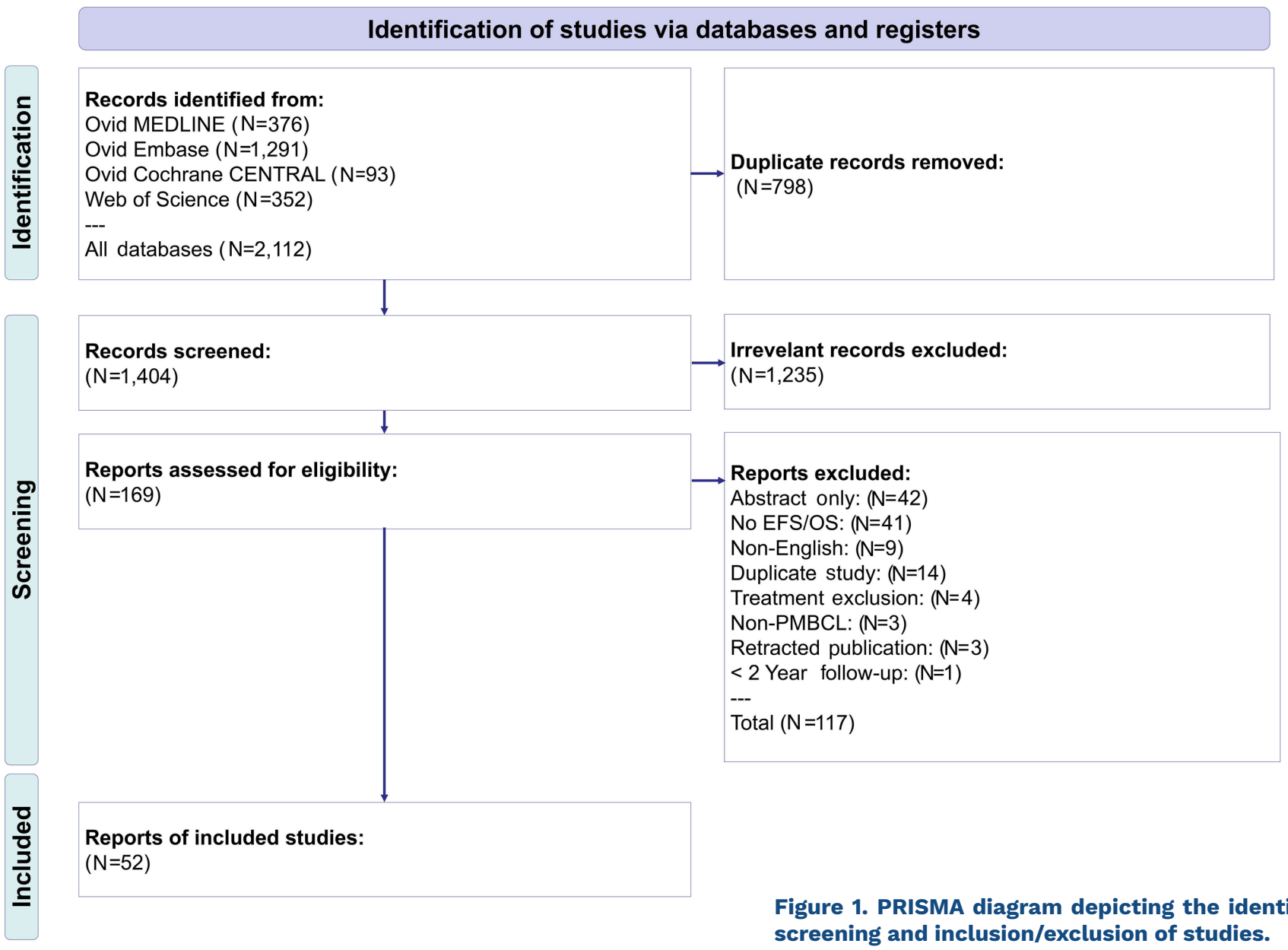

Figure 1. PRISMA diagram depicting the identification, screening and inclusion/exclusion of studies.

Table 1. Clinical characteristics of dose-intensive *versus* standard chemoimmunotherapy cohorts.

DI-CIT	N (%)	S-CIT	N (%)	*P**
Median age in years (range), N=1,860	32.8 (9-82)	Median age in years (range), N=1,307	33.8 (11-88)	<0.01
Female, N=1,838	1,112 (60.5)	Female, N=1,251	704 (56.3)	0.02
Stage, N=1,773 I - II III-IV	 1,201 (67.7) 572 (32.3)	Stage, N=1,244 I - II III-IV	 879 (70.7) 365 (29.3)	0.10
B symptoms, N=1,526	628 (41.2)	B symptoms, N=1,089	377 (34.6)	<0.01
Bulky disease, N=1,832	1,331 (72.7)	Bulky disease, N=1,242	779 (62.7)	<0.01
LDH > ULN, N=1,441	1,119 (77.7)	LDH > ULN, N=1,159	829 (71.5)	<0.01
Pleural effusion, N=913	320 (35.0)	Pleural effusion, N=270	89 (33.0)	0.58
Pericardial effusion, N=824	224 (27.2)	Pericardial effusion, N=245	56 (22.9)	0.20

Clinical characteristics for patients that were treated with dose-intensive chemoimmunotherapy (DI-CIT) compared to standard approach chemoimmunotherapy (S-CIT). Clinical characteristics for publications that were not divided by specific CIT regimen and pediatric only studies are reported separately in the *Online Supplementary Appendix*. **P*-value from *t* test or χ^2 test. N: number; LDH: lactate dehydrogenase; ULN: Upper Limit of Normal.

Table 2. Characteristics of dose-intensive *versus* standard approach chemoimmunotherapy.

DI-CIT	**N=2,517**
Rituximab-DI-CIT	1,522
da-EPOCH-R	670
VACOP/MACOP-B +/-R	458
2nd/3rd gen. chemo	375
IPR	329
R-CHOP-14/R-CHOEP-14	199
R-ACVBP	180
Front-line auto-SCT	141
GMALL	78
R-CHOP/R-ICE	49
R-HCVAD	38
S-CIT	**N=1,551**
R-CHOP-21	1,095
CHOP-21	456

Chemoimmunotherapy regimens included in both cohorts. DI-CIT: dose-intensive chemoimmunotherapy; S-CIT: standard approach chemoimmunotherapy; a-EPOCH-R: dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; VACOP-B: etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; MACOP-B: methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOEP: rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; R-ACVBP: rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone; GMALL: German multicenter ALL protocol; R-ICE: rituximab, ifosfamide, carboplatin, etoposide; HCVAD: hyper-cyclophosphamide, vincristine, doxorubicin, dexamethasone; 2nd/3rd gen. chemo: second-/third generation chemotherapy (MACOP-B, VACOP-B, ProMACE, CytaBOM); IPR: intensive pediatric regimens; auto-SCT: autologous stem cell transplantation.

(n=1,522) received rituximab-containing regimens compared to 70.6% (n=1,095) of the S-CIT cohort.

Median follow up was 56 months for both the DI-CIT and S-CIT cohorts. The test for homogeneity of proportions across DI-CIT and S-CIT studies (Figures 2, 3) was significant (P<0.01), depicting heterogeneity across the studies, thus the random effect model was employed. The lone exception was the analysis of rituximab-DI-CIT, which was found to have no significant heterogeneity (P=0.38), so the fixed effect model was used. Primary outcome data revealed a pooled overall survival of 88% (95% CI: 85-90) for the dose-intensive treatments, compared to 80% (95% CI: 74-85) for the S-CIT group (Table 3, Figure 2). Meta-regression analysis revealed an 8% survival benefit for the DI-CIT group (P<0.01). Key secondary outcome analysis (Table 3, *Online Supplementary Figure S1*) found a preserved survival advantage for rituximab-DI-CIT (pooled OS 91%, 95% CI: 89-93) compared to R-CHOP-21 (pooled OS 86%, 95% CI: 82-89). Meta-regression revealed a 4% survival benefit for patients treated with ritximab-DI-CIT (P=0.03). Pooled PFS was 83% (95% CI: 79-86) for the DI-CIT group, compared to 72% (95% CI: 65-79) for patients treated with S-CIT (Table 3, *Online Supplementary Figure S3*). Meta-regression predicted a 13% higher proportion of PFS for the DI-CIT group (P<0.01). Finally, consolidative mediastinal radiation (Table 3, Figure 3) was administered to 22% (95% CI: 15-31) of patients treated with dose-intensive regimens, compared to 55% (95% CI: 43-65) of R-CHOP-21/CHOP-21. Meta-regression analysis reported patients in the DI-CIT arm had a 24% reduced rate of receiving mediastinal radiation (P<0.01).

Investigation of da-EPOCH-R compared to R-CHOP-21 found a pooled OS of 90% (95% CI: 88-93) compared to 86% (95% CI: 82-89) and a PFS of 83% (95% CI: 78-87) and 77% (95% CI: 72-82), respectively (Table 3, *Online Supplementary Figures S2, S4*). Meta-regression analysis of these endpoints did not show a statistically significant difference when follow-up time was held constant. Consolidative mediastinal radiation was administered to 13% (95% CI: 7-21) of the da-EPOCH-R patients, compared to 57% (95% CI: 43-70) of the R-CHOP-21 arm (Table 3, *Online Supplementary Figure S5*). Meta-regression estimated a 42% reduction in consolidative RT for patients treated with da-EPOCH-R (P<0.01).

Discussion

Primary mediastinal B-cell lymphoma is a rare, aggressive B-cell lymphoma. While cure rates are high with chemoimmunotherapy, controversy remains regarding the optimal management and in particular the benefit of dose-intensity *versus* standard R-CHOP-21. Early retrospective studies led by Italian investigators demonstrated improved responses and outcomes with dose intensive approaches such as MACOP-B and VACOP-B when compared to CHOP-21.[56] Subsequent single-arm prospective[20] and retrospective[3,24] experiences reproduced excellent results with a variety of DI-CIT regimens. Despite this, obtaining prospective randomized data has been a challenge due to the rarity of the disease. Identifying the optimal approach is critical given that the disease typically affects the AYA population, and primary refractory or relapsed cases are challenging to cure.[61] Another important therapeutic consideration is the use of consolidative mediastinal radiation. This was historically a standard part of front-line treatment for PMBCL and continues to be used with significant frequency, particularly following R-CHOP-21. It is now well established from childhood cohort studies that mediastinal radiation use in the pediatric and AYA population significantly increases risk of secondary tumors[62] and cardiac disease.[63,64] Specifically, the risk of breast cancer beyond ten years of receiving mediastinal radiation in a similar population

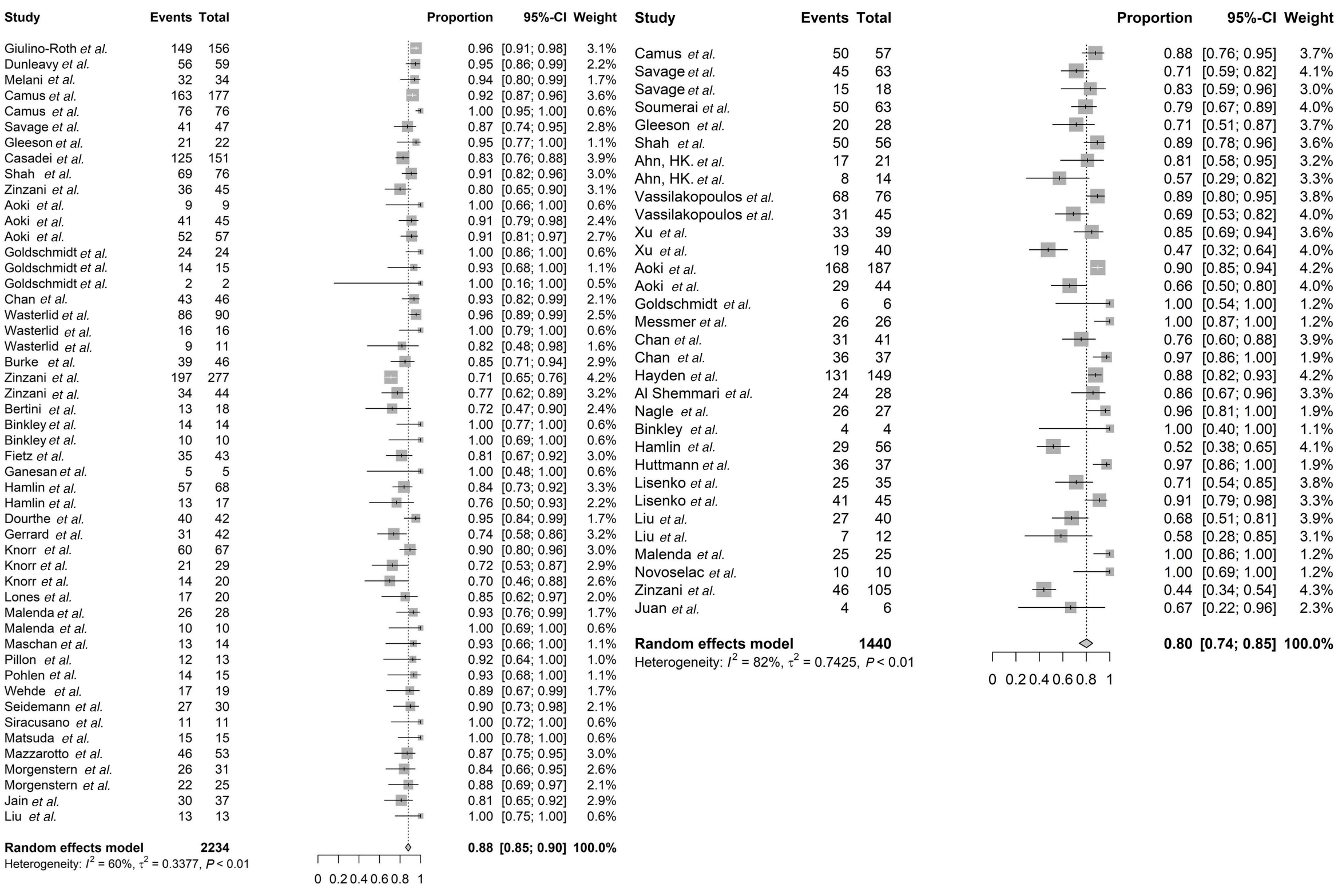

Figure 2. Forest plot comparing pooled overall survival for dose-intensive chemoimmunotherapy (DI-CIT) (left) and standard approach chemoimmunotherapy (S-CIT) (right) studies. Patient survival is recorded as the event next to total number of patients for each study.

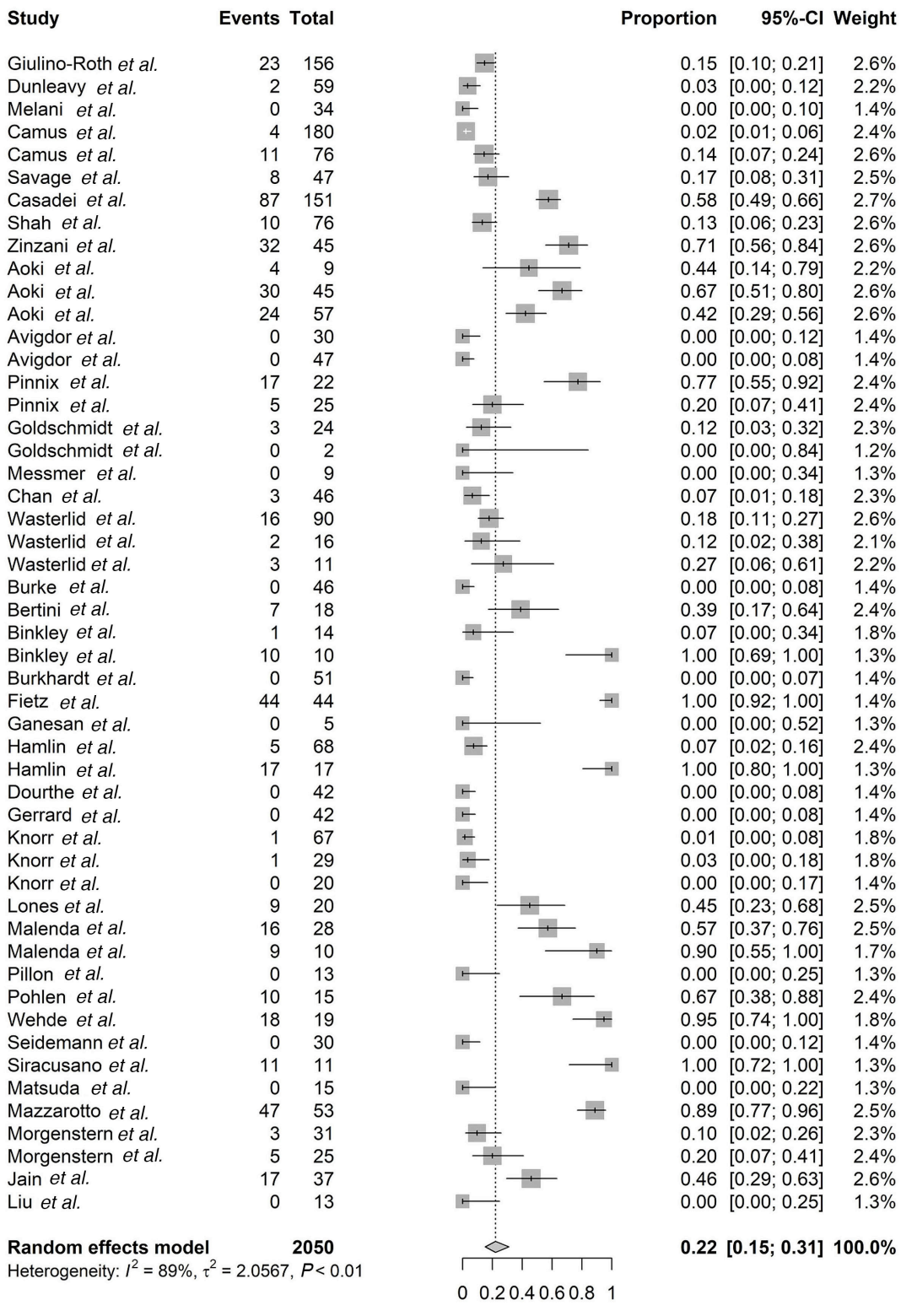

Figure 3. Forest plot comparing pooled consolidative mediastinal radiation for dose-intensive chemoimmunotherapy (DI-CIT) (left) and standard approach chemo-immunotherapy (S-CIT) (right) studies. Use of radiation is recorded as the event next to the total number of patients for each study.

is notably high, with a reported incidence of 35% among childhood Hodgkin lymphoma survivors.[2] Therefore, using strategies that achieve high cure rates and at the same time obviate the need for mediastinal radiation with its associated toxicities is a key priority for advancing PMBCL therapeutics. Consequently, the goal of our systematic review and meta-analysis was to analyze all available published data comparing S-CIT *versus* DI-CIT to inform on the optimal approach in treating newly diagnosed PMBCL. Survival and progression-free outcomes appear to favor dose-intensive therapy upon analysis of 4,068 patients with newly diagnosed PMBCL. Pooled overall survival was superior for DI-CIT (88% [95% CI: 85-90]) compared to S-CIT (80% [95% CI: 74-85]) with meta-regression demonstrating an 8% OS benefit for the DI-CIT group (P<0.01). Notably, this survival advantage held when comparing rituximab-DI-CIT (91%, 95% CI: 89-93) to R-CHOP-21 (86%, 95% CI: 82-89; P=0.03) hypothesizing that the intensity of the underlying chemotherapy backbone is vital to achieve the best possible treatment outcome in patients with PMBCL. Pooled PFS was also significantly higher for the DI-CIT group (83% *vs.* 72%; meta-regression 13% PFS benefit, P<0.01). Importantly, there was a much lower rate of reliance on consolidative mediastinal radiation in the DI-CIT arm; only 22% received RT, compared to 55% in the S-CIT arm. We would hypothesize that less radiation exposure will curtail incidence of secondary malignancy and ischemic heart disease; however, this study was unable to statistically answer this important question, as included evidence did not follow patients long enough (median follow-up: 56 months) to reliably analyze chronic toxicity. We also acknowledge that our study was not designed to assess the differences in toxicity between the two cohorts. DI-CIT has been reported to increase acute toxicity, such as febrile neutropenia, infection, mucositis and peripheral neuropathy compared to R-CHOP-21.[3,65] The comparative risk of chronic toxicity such as secondary malignancy or cardiotoxicity of DI-CIT and S-CIT +/- RT remains an important unknown that will require further dedicated investigation.

Secondary outcome analysis found numerically higher OS (90% *vs.* 86%) and PFS (83% *vs.* 77%) for patients treated with da-EPOCH-R (n=670) compared to R-CHOP-21 (n=1,095), although these endpoints did not meet statistical significance on meta-regression analysis. Dose-adjusted EPOCH-R allowed for only 13% of patients to require consolidative RT, a 42% reduction (meta-regression P<0.01) when compared to R-CHOP-21 treatment protocols. Despite the lack of statistical survival benefit, the favorable numerical survival and infrequent radiation use would suggest a strong net benefit for da-EPOCH-R compared to R-CHOP-21.

These results support the aforementioned retrospective[3,24] and single arm prospective[20,66] landmark studies of DI-CIT, and highlight the vital concept that dose-intensive treatment is associated with less disease progression and death from PMBCL. Our results also align with recently presented conference abstracts reporting excellent outcomes for DI-CIT in PMBCL.[67,68] Additionally, our study highlights that patients treated with S-CIT had less bulky disease (62.7% *vs.* 72.7%; P<0.01), lower rates of B-symptoms (34.6% *vs.* 41.2%; P<0.01) and lower median LDH levels (71.5% *vs.* 77.7%; P<0.01), suggesting a more favorable patient population who nevertheless had inferior outcomes compared to

Table 3. Primary and secondary outcomes.

Treatment cohort	Overall survival, % (95% CI)	Meta-regression *P*
DI-CIT, N=2,234	88 (85-90)	< 0.01
S-CIT, N=1,440	80 (74-85)	
da-EPOCH-R, N=636	90 (88-93)	< 0.25
R-CHOP21, N=1,032	86 (82-89)	
R-DI-CIT, N=1,279	91 (89-93)	0.03
R-S-CIT, N=1,032	86 (82-89)	
Progression-free survival, % (95% CI)		
DI-CIT, N=1,501	83 (79-86)	< 0.01
S-CIT, N=1,200	72 (65-79)	
da-EPOCH-R, N=276	83 (78-87)	0.18
R-CHOP21, N=957	77 (72-82)	
Consolidative radiation, % (95% CI)		
DI-CIT, N=2,050	22 (15-31)	<0.01
S-CIT, N=1,202	55 (43-65)	
da-EPOCH-R, N=670	13 (7-21)	<0.01
R-CHOP21, N=894	57 (43-70)	

Primary and secondary outcome data for different treatment cohorts. Meta-regression analysis was performed for each endpoint, compared dose-intensive chemoimmunotherapy (DI-CIT) *versus* standard approach chemoimmunotherapy (S-CIT), da-EPOCH-R *versus* R-CHOP21 and rituximab-containing DI-CIT *versus* S-CIT only. da-EPOCH-R: dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

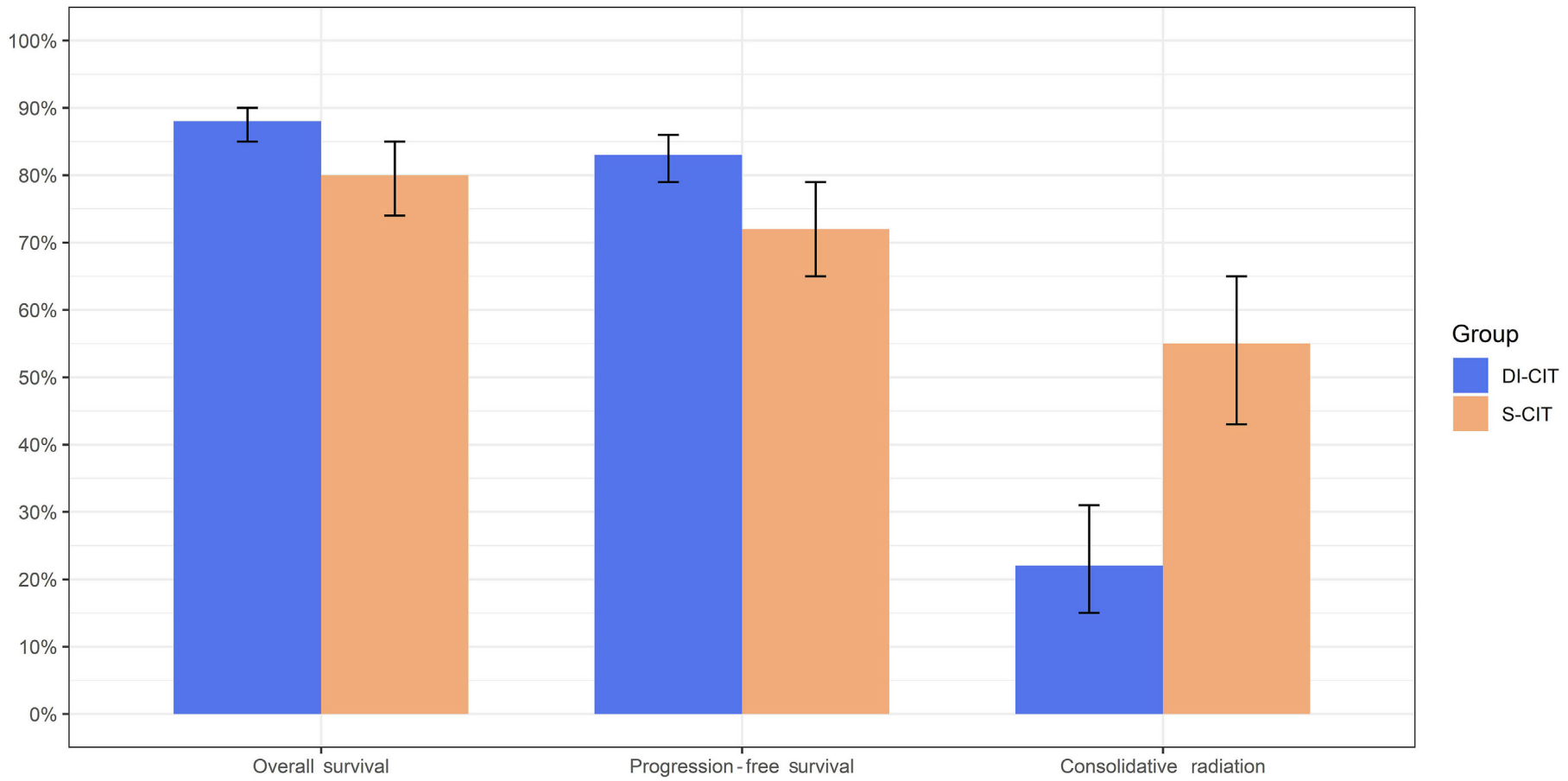

Figure 4. Graphical representation of the pooled primary and secondary outcomes for patients treated with dose-intensive chemoimmunotherapy (DI-CIT) compared to standard approach chemoimmunotherapy (S-CIT).

the DI-CIT group. Finally, the standard CIT group received more rituximab containing regimens (70.6% *vs.* 60.5%), which further strengthens the survival advantage seen in the DI-CIT cohort.

Our study's principal limitation is that it is a meta-analysis and not a prospective randomized comparative trial, which would be the ideal setting to answer the question of benefit of DI-CIT over S-CIT in PMBCL. Currently, the IELSG-37 trial is prospectively evaluating the role of consolidative radiation in PMBCL and additionally assessing the impact of different induction regimens on outcome in PMBCL. In line with our findings, an early report from IELSG-37, demonstrated inferior outcomes with R-CHOP-21 compared to dose-dense/dose-intensive regimens.[69] A more recent update of the trial demonstrated patients in complete remission by FDG-PET imaging at the end of therapy had no difference in OS when randomized to observation *versus* radiotherapy.[70] We look forward to the final published analysis with a focus on survival outcomes stratified by chemoimmunotherapy regimen. Another inherent limitation to meta-analysis is the heterogeneity of the data included, which was highlighted in our study with the Cochran's Q and I^2 statistics. The practical impact of heterogeneity statistics depends on the size and direction of treatment effect.[7] Given our large sample size, similar heterogeneity and direction of both treatment outcomes, and large statistically significant survival and radiation benefit for the DI-CIT treatment protocols, we perceive these results to be impactful regardless of the heterogeneity statistic. Available evidence of treatment for PMBCL is by definition heterogeneous; to develop a sizeable dataset in a rare disease clinicians must collect data across a lengthy timeline, wherein medical advances change standard of care practice. Two concrete examples in PMBCL would be the widespread implementation of rituximab in B-cell lymphomas, as well as the use of PET/CT scans for disease responsiveness. Many of our included datasets report outcomes before and after the application of these tools; excluding these studies would have impacted the size and strength of this analysis. Finally, data used for this analysis are summarized published information, which is less reliable than individual patient's statistics from each publication dataset.

In conclusion, to our knowledge this study is the largest systematic review and meta-analysis looking to combine the aforementioned published data to evaluate if dose-intensive CIT improves outcomes in PMBCL. As we await prospective randomized data (clinicaltrials.gov identifiers NCT01599559 and NCT04759586) our findings suggest that dose-intensive CIT alone should be the preferred approach in the management of patients with newly diagnosed PMBCL as it is associated with higher survival outcomes and significantly less reliance on mediastinal radiation.

Disclosures

KD served on the advisory board/consulting for AstraZeneca, Beigene, AbbVie, Daiichi Sankyo, ADC Therapeutics, Incyte, Morphosys, Genmab, Cellectar, and has received research funding from Kymera, ONO, Genentech, Merck. MRC, LSW, CSD, YL and KM have no conflicts of interest to disclose.

Contributions

MRC and KD designed the study concept and methodology. CSD carried out the systematic review using pre-specified keywords and template publications (supplied by MRC and KD) to be included in the analysis. MRC and LSW reviewed the systematic literature search, applying inclusion/exclusion criteria, and extracting data from included publications. YL and KM performed all the statistical analysis. All authors contributed to writing the manuscript and/or editing.

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Data-sharing statement

For original data, please refer to the references that were included within the meta-analysis. For our extracted conglomerate datasets please contact Michael.Cook@pennmedicine.upenn.edu

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