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The Role of Radiotherapy in Relapse/Refractory Diffuse Large B-Cell Lymphoma in the Rituximab Era: A Systematic Review and Meta-Analysis

Research Article

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Abstract

Purpose: The role of radiotherapy (RT) in the salvage setting for patients with relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL) is unclear in the rituximab era. We sought to determine the efficacy and toxicity of RT for this group of patients.

Methods: We searched various biomedical databases, including conference proceedings, for eligible studies where patients were treated with salvage radiotherapy for r/r DLBCL after receiving rituximab based chemotherapy regime. Random-effects meta-analysis with inverse variance weighting to pool prevalence data was performed. Outcomes of interest were 2 and 5-year overall survival (OS-2, OS-5), 2 and 5-year progression free survival (PFS-2, PFS-5) and Grade 3 or 4 adverse events (AE). Study quality was assessed using the Newcastle-Ottawa scoring system.

Results: We found 12 eligible non-comparative studies including 387 patients who received rituximab based chemotherapy as first line treatment and subsequently relapsed or had residual disease on post treatment restaging imaging. The OS-2 and OS-5 was 90% (95% CI, 84 – 95%) and 83% (95% CI, 76 – 89%) respectively. Similarly, PFS-2 and PFS-5 were 81% (95% CI, 72 – 90%) and 74% (95% CI, 65 – 82%) respectively. Sub-group analysis showed that studies with prospective design had higher rates of OS-2 and OS-5 compared with studies of retrospective design (OS-2: 97% vs 81%, interaction P (IP) = 0.009; OS-5: 95% vs 75%, IP = 0.003). and studies with peri-transplant RT had lower rates of OS-5 compared to studies with salvage RT alone (59% vs 77%, IP = 0.03).

Conclusion: The available evidence, albeit low quality, suggests that salvage radiotherapy provides encouraging disease control and survival rates. It also emphasizes the need for high-quality randomized trials to establish how RT can be integrated optimally in this setting.

Keywords: Radiotherapy; Relapsed; Refractory; Diffuse large B-cell lymphoma; Salvage

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of Non-Hodgkin lymphoma (NHL), comprising of 30 – 40% of all cases [1,2]. The outcomes of DLBCL have improved significantly with the introduction of the anti-CD20 antibody rituximab [3]. First-line treatment for DLBCL is routinely with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone) or equivalent regimens, with the addition of consolidation radiotherapy (RT) for early stage (ES) or high risk disease such as bulky or skeletal

involvement [2,4-6]. Despite this, up to 40% of these patients will have either primary refractory or relapse (r/r) disease after achieving initial complete response (CR) [7]. In this setting, salvage chemotherapy followed by autologous stem cell transplant (ASCT) has been shown to be more effective than salvage chemotherapy alone, in both the pre- and post-rituximab era [8,9]. In the final analysis of the Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL), patients who received ASCT demonstrated a 4-year progression free survival (PFS) and 4-year overall survival (OS) of 56% and 65% respectively [8]. However, it must be highlighted that at least two thirds of patients with r/r DLBCL were not eligible for ASCT [9]. This is has been attributed to a number of factors such as age and comorbidities which are associated with early toxicities, including engraftment syndrome and transplant related mortality [9]. Hence, for this group of patients, there are limited salvage options with the majority being enrolled in clinical trials, involving novel therapies [9].

Historically, radiotherapy (RT) has proven to be a highly efficacious and cost-effective modality for the treatment of lymphoma. When RT has been combined with chemotherapy with or without rituximab for the treatment of DLBCL, outcomes have significantly improved [10,11]. For r/r DLBCL, the PARMA trial randomized chemotherapy-sensitive relapsed DLBCL patients in the pre-rituximab era to either salvage chemotherapy alone or in combination with ASCT; up to 40% of patients in the trial received RT as part of their salvage treatment [12]. Fewer relapses were reported among the irradiated patients (36% vs 55%), despite the presence of bulky disease in the RT group, adding further support for the role of RT in the salvage setting [9,12]. Whilst there are no published randomized trials of RT in the rituximab era to guide treatment decisions, a retrospective study with 469 patients demonstrated a significant improvement in OS and PFS in those who had received consolidation RT [13]. For patients with early stage disease, the 5-year OS and PFS with RT were 92% and 82% respectively compared to 73% and 68% in those who did not receive consolidation RT [13]. Similar trends were noted in advanced stage disease treated with consolidation RT (5-year OS = 89% vs 66% and 5-year PFS = 76% vs 55%). In addition, RT related toxicities have also been significantly reduced as modern concepts, such as reduction in dose and treatment volume, incorporation of functional imaging, motion management and image-guidance strategies, are being adopted [14].

To date, there are no randomized studies investigating the role of RT in the salvage setting and studies have been heterogeneous in nature. To address this, the International Lymphoma Radiation Oncology Group (ILROG) have offered recommendations based on a number of studies reporting outcomes of patients with relapsed or refractory disease [9]. Despite the inclusion of studies from the pre-rituximab era and the fact that studies were heterogeneous, a significant improvement in local control and overall survival in those who received salvage RT was apparent [14]. Although several salvage options for r/r DLBCL are available, the role of RT in this setting is not well defined, especially in the rituximab era. We therefore aim to address this issue by performing a systematic review and meta-analysis to quantify the treatment effect of salvage RT in those individuals who had relapsed/ refractory disease post upfront rituximab-based regimens. This will allow a better selection of patients in future studies and allow for optimal integration of salvage RT into the evolving landscape of treatment options and clinical trials.

Materials and Methods

Search strategy and selection criteria for studies

We conducted a search of the following electronic databases from June 2000 to January 2019 MEDLINE (via PubMed), EMBASE and the Cochrane Library. A search strategy was developed based on a combination of subject headings and keywords related to the concept of "radiotherapy", "relapse or refractory diffuse large B-cell lymphoma" and "rituximab". We limited the search to studies published in English and involving human subjects only. We also searched the reference lists of identified studies for relevant articles. The detailed search strategy was included as shown by Figure 1. We defined refractory/ relapse DLBCL (including subtype primary mediastinal B–cell lymphoma) as stable or progressive disease that received at least 4 cycles of first-line chemotherapy with Rituximab [15]. We excluded studies that received consolidation RT as part of first line treatment or received consolidation RT but did not receive a rituximab based first line therapy.

Two authors independently screened the titles and abstracts that fulfilled the following inclusion criteria: (1) included patients who received a rituximab-based regimen as first line (2) histologically and/ or radiologically proven relapse/ refractory DLBCL including Primary Mediastinal Lymphoma (PMBCL); (3) reported outcomes of interest at least 2-year and 5-year survival (i.e. progression free survival, overall survival, and toxicities); and (4) an original study (i.e., randomized controlled trial [RCT], cohort studies, observational studies, or case series).We excluded primary central nervous system lymphoma (PCNSL), non-original studies such as reviews, case reports and studies with a sample size of less than 10.

Data collection and extraction

Two reviewers further evaluated the search results independently. The full texts of articles that met the inclusion criteria were retrieved for further evaluation. Discrepancies in selection were resolved by consensus after detailed discussions. The same two reviewers then extracted the data independently using standardized data collection forms. Data that were collected included publication details, methodologies, sample sizes, demographic data, median follow-up, median time to relapse/refractory, initial Stage Early (1 and 2) versus Late (3 and 4), International Prognostic Index (IPI) score, presence of bulky disease, presence of extra nodal sites, primary mediastinal B-cell lymphoma, received rituximab based first line chemotherapy, RT for salvage treatment, peri-transplant RT, 2 and 5-year OS and PFS, G3 toxicity and above, Agency for Healthcare Research and Quality (AHRQ) standards (Good, Fair, Poor).

Data quality assessment

We assessed the quality of each study with the Newcastle-Ottawa Quality Assessment form. This assessment was broadly based on study type, selection criteria of study groups, comparability of study participants and metrics used to measure outcomes. Each study is given a final grade of poor, fair or good based on the overall confounding bias and robustness of data.

Statistical analysis

We calculated the event rates for the outcomes of interests and estimated the 95% confidence interval (CI) using the Jeffreys method [16]. Individual log-transformed event rates and their variances were combined using the generic inverse variance method. We performed the meta-analysis using the Cochrane Collaboration software (RevMan, version 5.3; http://www.cochrane.org). We carried out the primary analyses with Der Simonian and Laird random effects model, and assessed statistical heterogeneity of the combined results with the I^2 index, with a value of <25% being interpreted as a low level of heterogeneity [17,18].

Subgroup analysis

Subgroup analyses were performed to determine if the results were influenced by type of study (prospective vs retrospective), subtype of DLBCL (DLBCL vs PMBCL), and use of peri-transplant RT. Interaction tests were used to compare the differences between estimates from different subgroups (Figure 1) Table 1.

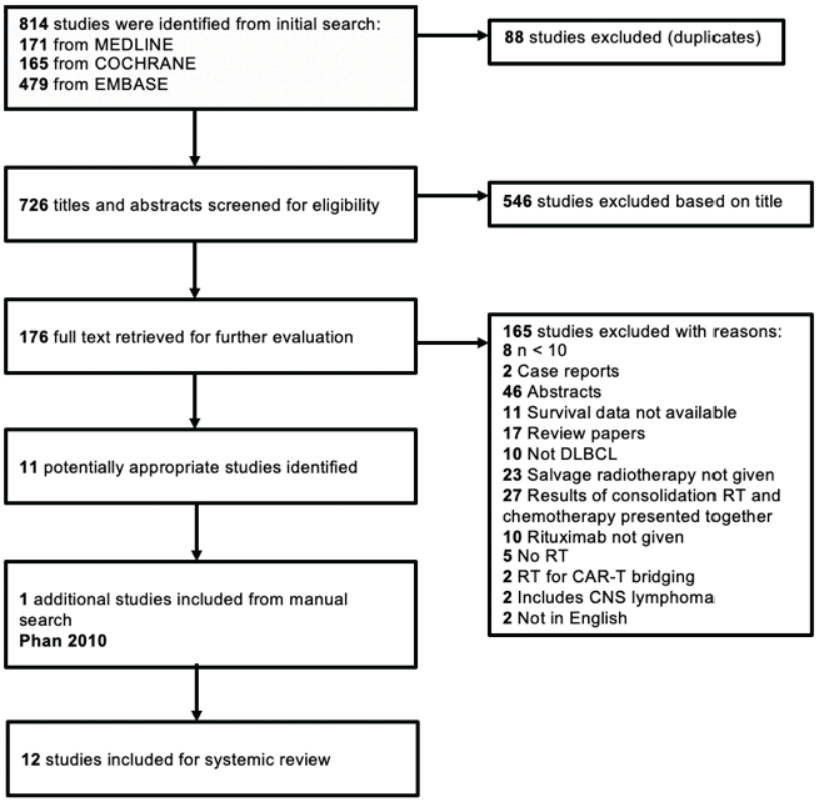

Figure 1: Results of search strategy.
Abbreviations: RT: Radiotherapy; CAR-T: Chimeric Antigen Receptor T Cells

Table 1: Characteristics of studies using salvage radiotherapy for r/r DLBCL.

Study/Design	Study Period	N	Criteria used to Define r/r DLBCL	RT Field	Description of RT Dose Planning	Toxicity G3+ (%)	Study Quality
Biswas 2010[7] (Retrospective)	1992-2005	13	Not mentioned. Refractory if they never achieved a CR following initial therapy or relapsed if at least one CR was achieved prior to ASCT.	Post ASCT IFRT	CR to salvage chemotherapy generally received 20 to 26 Gy Persistent disease post salvage chemotherapy 30 to 36 Gy.	NR	Poor
Broccoli 2017[28] (Retrospective)	1989-2010	37	SUV values not mentioned. Nodal residues larger than 1.5 cm which have regressed by more than 75% in their major diameter were compatible with CR, and regarded as residual scar tissue. PET negativity was corroborative of a CR.	NR	Positive PET-scan post chemotherapy or bulky disease at onset. Received 30 to 36 Gy	NR	Fair
Chan 2019[29] (Retrospective)	2001-2016	40	CT or FDG-PET based on lugano classification.	NR	NR	NR	Fair
Chin 2017[30] (Retrospective)	2003-2015	16	DS 1–2 indicates a CR, DS 3 is equivocal, and DS 4 or 5 indicates FDG-PET positive residual/progressive disease.	NR	Median dose 40 Gy	NR	Fair
Dabaja 2014[21] (Retrospective)	2001-2007	13	Patients with a residual mass on CT were considered in remission if no FDG avid activity was detected on PET/CT. Partial remission was defined as >50% regression of CT findings at 1 or more previously involved sites with positive PET. Stable disease was defined as <50% regression of CT findings or no change with positive PET.	IFRT	36 Gy to initial bulky sites (7.5 cm)	NR	Fair
Dorth 2010[31] (Retrospective)	1996-2007	13	Patients achieving a negative interim PET/gallium scan did not routinely have functional imaging carried out at the completion of chemotherapy. All patients who had a positive interim PET/gallium scan had an additional study carried out at least 2 weeks after the last cycle of chemotherapy. positive or negative based on visual analysis alone, based on consensus recommendations of the International Harmonization Project in Lymphoma	ISRT	The median radiation dose to all sites was 30 Gy (15–45 Gy). Median RT dose for patients with a positive PET was higher than those with a negative scan (36 versus 30 Gy)	NR	Fair

Lamy 2018[19] (Prospective)	2005-2014	38	PET positivity was defined visually as 18F-Fluorodeoxyglucose (18F-FDG) uptake above mediastinum or surrounding background in a location incompatible with normal anatomy or physiology. A negative scan was defined as having no abnormally increased 18F-FDG at any site.	IFRT	40 Gy in 20 fractions	7.80%	Good
Grignano 2018[32] (Retrospective)	2003-2017	51	Not mentioned	IFRT, INRT and ISRT	Bulky >7cm 40 Gy in 20 fractions	NR	Good
Hoppe 2009[33] (Retrospective)	2000-2007	47	Biopsy-proven disease within 30 days of finishing first-line therapy, relapsed (evidence of disease 430 days after finishing first line therapy.	IFRT	30 Gy in 20 fractions BID	6.3% Radiation enteritis = 2 Pneumonitis = 2	Fair
Sert 2018[34] (Retrospective)	2008-2014	42	Pretreatment FDG-PET (FDG-PET) images were used for evaluation, and cutoff value for maximum standardized uptake values (SUVs) was selected as 13 according to the recommendations.	ISRT	Total radiation ranged from 30.6–45 Gy with 1.8 Gy daily fractions. Radiation dose was 30.6 Gy for those with no residual disease at FDG-PET and CT scan, and the dose was up to 45 Gy in the patients with non-metabolic residual disease at FDG-PET/CT scan.	NR	Poor
Holzhauser 2017[35] (Retrospective)	2005-2015	34	Patients had pre-and post-PET/CT. CR was defined as disappearance of any identifiable pre-chemotherapy lymphatic spread on CT or presence of some residual disease on CT that was negative on PET-CT. PR was defined as ≥ 50% regression of measurable disease without presence of new sites of disease.	ISRT	40 Gy in 20 fractions	None (3 patients developed grade II late side effects (xerostomia, pneumonitis, pylorus stenosis)	Fair
Phan 2010[13] (Retrospective)	2001-2017	43	PET SUVs were grouped as ≤ 13 or more than 13. More than 13 predicted for more aggressive disease. CR was defined as the complete disappearance of all detectable clinical and radiographic disease on both PET scan and diagnostic CT; patients with negative PET but with residual disease on diagnostic CT were considered in an unconfirmed CR. PR was defined as ≥ 50% reduction in tumor bulk; stable disease (SD) e was defined as less than a partial remission but not progressive disease. Progressive disease requires a ≥ 50% increase in the sum product of the greatest diameters of any previously identified abnormal lymph node or mass or the appearance of any new lesion during or at the end of therapy.	IFRT	The dose of radiation ranged from 30 to 39.6 Gy according to the bulk of disease. 36 to 39.6 Gy if tumor > 5 cm and/or residual disease could still be detected on CT with a negative PET	NR	Fair

Abbreviations: R: Retrospective; P: Prospective; PFS: Progression Free Survival; RT: Radiotherapy; IFRT: Involved field RT; ISRT: Involved Site RT; INRT: Involved nodal RT; NR: Not Reported; ORN: Osteoradionecrosis; ASCT: Autologous Stem Cell Transplant; PET: Positron Emission Tomography; FDG: F-Fluorodeoxyglucose; CR: Complete Response; PR: Partial Response; SD: Stable Disease; DS: Deuville Score

Results

Results of search strategy and characteristics of included studies

We identified 814 studies, and of these, 88 were excluded as they were duplicates and a further 564 were excluded as they did not fulfil the inclusion criteria at the initial screening of their titles and abstracts. Of the 176 studies for which full texts were reviewed, 165 were excluded as they were irrelevant or did not meet the inclusion criteria (Figure 1). We found 12 eligible non-comparative studies including 387 patients. We found two studies that had used peri-transplant RT and three studies involving PMBCL. Only one study was of prospective design and the rest of 11 studies were retrospective in nature.

The median time to follow-up of the included studies was 40 months (IQR: 32 – 46 m). The median age of the study participants was 54 years (IQR: 46 – 61). Two hundred two (49%) participants were initially diagnosed as early stage I or II and 103 (25%) were late stage III or IV. Bulky disease was observed in 145 (35%) participants. Based on International Prognostic Index (IPI) score at diagnosis, 135 (33%) had low IPI score (0 – 1) and 30 (7.4%) had extra nodal site involvement. Based on histology, 127 (31%) were reported as PMBCL. We found 75 participants (18%) that underwent ASCT and had peri-transplant

RT. Finally, we found only 20 (5%) participants received concurrent chemotherapy or biologic treatment together with RT. Overall, RT related toxicities of Grade 3+ were poorly reported with only three studies reporting toxicity rates Figure 2 & Figure 3.

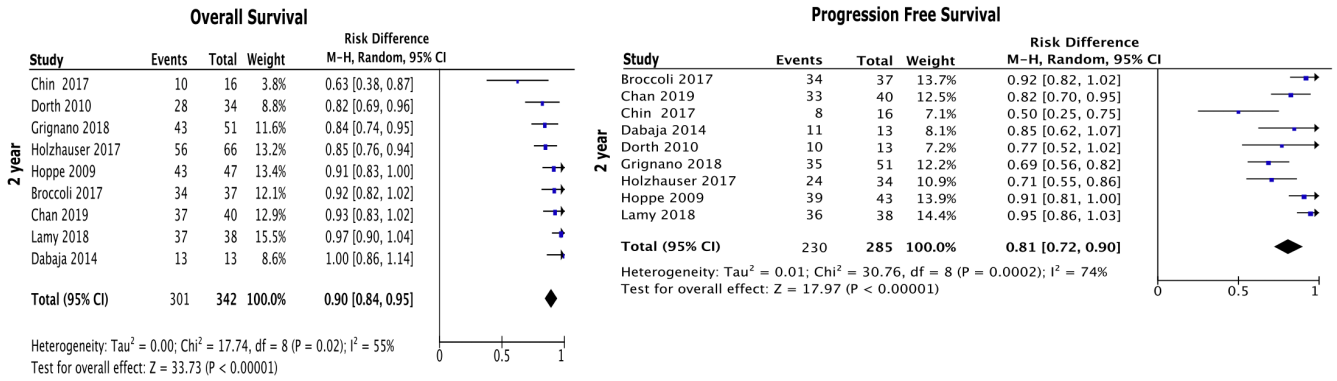

Figure 2: Pooled event rate for 2-year overall and progression free survival. Forest plot for odds ratios of 2-year overall and progression free survival.

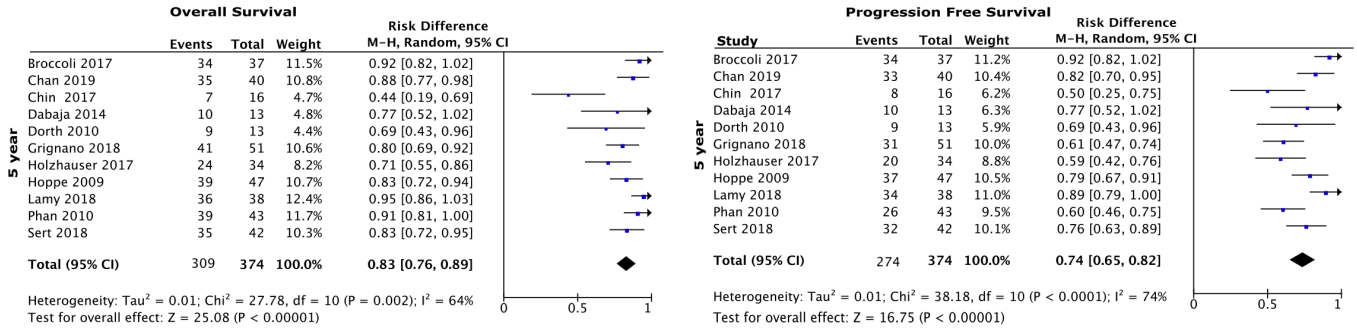

Figure 3: Pooled event rate for 5-year overall and progression free survival. Forest plot for odds ratios of 5-year overall and progression free survival.

Survival and subgroup analysis

At 2 years, salvage RT was associated with an OS rate of 90% (95% CI, 84 – 95%, I^2 = 54%) and PFS rate of 81% (95% CI, 72 – 90%, I^2 = 74%) from a sample size of 342 and 285 patients respectively as shown by figure 2. At 5 years, we found an OS rate of 83% (95% CI, 76 – 89%, I^2 = 64%) and PFS rate of 74% (95% CI, 65 – 82%, I^2 = 74%) from 374 patients as shown by figure 3. Overall, Grade 3 or 4 AE rate was 8% (95% CI, 2 –14%, I^2 = 0%) in 102 patients. These results demonstrate significant heterogeneity amongst the studies with I^2 greater than 50% in different cohorts, hence it is difficult to make meaningful comparisons.

We performed pre-planned exploratory analyses of subgroup effects and compared three groups: DLBCL versus PMBCL, prospective studies versus retrospective studies and ASCT peri-transplant RT versus salvage RT alone as shown by Table 2. We found no significant differences in OS and PFS between DLBCL and PMBCL (OS-2: 88% vs 82%, IP = 0.17; OS-5: 76% vs 78%, IP = 0.91; PFS-2: 77% vs 80% IP = 0.75; PFS-5: 62% vs 77%, IP = 0.36). Additionally, the prospective study had a higher rate of OS-2, OS-5, PFS-2 and PFS-5 compared with the studies of retrospective design (OS-2: 97% vs 81%, IP = 0.002; OS-5: 95% vs 75%, IP = 0.003; PFS-2: 95% vs 76% IP = 0.002; PFS-5: 89% vs 64% IP = 0.002). We also noted Grade 3 – 4 toxicities were higher in the prospective group but this was not significant (8% vs 4%; IP = 0.4). Finally, studies which used peri-transplant RT on ASCT, had significantly lower rates of OS at 5 years, compared with studies that did not have ASCT (OS-5: 59% vs 79%, IP = 0.03) but there was no significant difference in PFS at 5 years (PFS-5: 79% vs 77%, IP = 0.33). This is likely attributed to a number of factors such as inherent heterogeneity in these patients where there will be selection biases for different treatments. This includes patient related factors and disease related factors such as the extent of disease (localized versus disseminated disease) and disease biology hence making such comparisons between peri-transplant RT vs salvage RT alone difficult here. In addition, no significant toxicities were observed in the peri-transplant RT group (1% vs 5%, IP = 0.21) Table 2.

Quality of summarized evidence

Using the Newcastle Ottawa quality assessment, 10 of 12 studies were rated as poor or fair quality highlighting significant methodological limitations. This is mainly due to the studies being retrospective in design. Two studies were rated as good quality studies.

Discussion

The optimal treatment for r/r DLBCL has not been well defined. Although RT is an effective modality in the management of lymphomas, its impact in the salvage setting, especially in the rituximab era, is not well determined; whether used alone or in combination with salvage systemic regimens. There are some guidelines from ILROG which advocate the use of RT in certain situations, such as to bridge patients for ASCT [9]. However, it has to be noted that most of the studies referenced in the guidelines were performed in the pre-rituximab era [9]. Our findings, based on studies in the rituximab era, are encouraging for the use of salvage RT, in terms of OS and PFS. We considered various scenarios including patients with r/r DLBCL receiving salvage RT alone, peri-transplant RT and r/r PMBCL. Pooled results indicate an excellent 2-year and 5-year OS (90% and 83% respectively) and PFS rate (81% and 74% respectively) for patients with r/r DLBCL who underwent salvage RT. Although toxicity was not reported uniformly, the overall toxicity rates of severe toxicity (Grade

3 – 4) were considered to be low (range 2 – 14%). Given most of these studies were retrospective, it is difficult to determine if these toxicities were truly due to salvage RT or from other treatments. Whilst there was a significant degree of heterogeneity amongst included studies (I^2 = 55 – 74%), we attempted to address this using pre-planned subgroup analysis. Our analysis showed significant improvement in OS and PFS of prospective study compared to retrospective studies (OS-2: 97% vs 81%, IP = 0.002; OS-5: 95% vs 75%, IP = 0.003; PFS-2: 95% vs 76% IP = 0.002; PFS-5: 89 vs 64 IP = 0.002). However, this has to be interpreted with caution as only one study utilized a prospective design [19]. Moreover, it is unclear if this finding is related to the higher proportion of early stage non-bulky disease or closer follow up that occurs with a prospective study design. Interestingly, no significant differences were noted in OS and PFS between DLBCL and PMBCL (OS-2: 88% vs 82%, IP = 0.17; OS-5: 76% vs 78%, IP = 0.91; PFS-2: 77% vs 80% IP = 0.75; PFS-5: 62% vs 77% IP = 0.36). This may be relevant in context of recent evidence showing equivalent efficacies of R-CHOP compared to R-DA-EPOCH chemotherapy regimens in DLBCL patients including PMBCL; where RT has been deemed unnecessary with the R-DA-EPOCH regimen [20]. We did not perform a subgroup analysis according RT dose, as we did not expect a large variability in RT dose, with most of the studies using between 30 – 40 Gy (Table 1).

The use of functional FDG-PET imaging to determine the use of salvage RT is controversial. The series from MD Anderson found a mid-treatment FDG-PET assessment to be prognostic value in patients with newly diagnosed DLBCL [21]. In addition, they support the addition of RT for patients who remain PET-positive on the mid-treatment assessment [21]. For example, PET-positive patients treated with chemotherapy alone achieved a 5-year OS of 51%, compared to patients who received consolidation RT achieving a 5-year OS of 81% [21]. Within the context of r/r/ DLBCL, FDG-PET response prior to ASCT has also shown to have prognostic value [22]. In this series, RT was used at the discretion of the treating physician, with approximately 40% receiving RT prior to ASCT [22]. However, unlike the earlier study, the use of RT did not improve the survival outcomes of patients, including those who remained PET-positive prior to ASCT [22]. These results should be interpreted with caution as only a small number of patients in the retrospective series received peri-transplant RT (54 of the 129 patients). Interestingly, our findings favour the use of salvage RT compared to previous studies which have shown conflicting results [23,24]. It is worth noting that these were older studies, where patients would have been treated with older radiation techniques with larger radiation fields and doses resulting in major radiation-related toxicities [23,24]. In view of this uncertainty, ILROG has come up with practical guidelines and specific case scenarios where salvage radiotherapy should be considered for r/r DLBCL [9].

At present, there are several novel therapies under development and investigation for r/r DLBCL that have shown encouraging objective response rates (ORR) of between 30 to 60% [25]. These include targeted therapies such as ibrutinib, checkpoint inhibitors, immunomodulators, combination agents and monoclonal antibody such as obinutuzumab and blinatumomab [25]. Despite this, median survival is still less than 6 months compared to 11.1 months in patients undergoing ASCT [25]. In addition, CAR-T cell therapy has shown promising results in this setting [26]. Recent studies have reported objective response rates ranging from 59-88% with about half achieving CR, with some lasting more than 2 years [26]. However, a significant proportion of patients (20 – 30%) in these studies experienced CAR T-cell-related toxicity with cytokine-release syndrome (CRS) and neurotoxicity [26]. Interestingly, LaRiviere's group has recently shown that induction RT prior to CAR-T cells can significantly reduce grade 3 CRS or neurotoxicity and may have a potential role as a bridging and cytoreduction strategy [27]. From the above, it is evident that the landscape of novel agents is evolving rapidly. However, at present, there is limited long-term outcome and toxicity data with such approaches. As such, we should consider integrating these options judiciously with currently established effective strategies in order to maximize cost-effectiveness and patient benefit [28].

Table 2: Subgroup analysis.

Subgroup	2Y OS	5Y OS	2Y PFS	5Y PFS	G 3+
DLBCL	88% (80 – 95%)	76% (66 – 87%)	77% (65 – 89%)	62% (41 – 83%)	5% (1 – 8%)
PMBCL	82% (62 – 102%)	78% (55 – 100%)	80% (64 – 97%)	77% (53 – 100%)	3% (4 – 9%)
Interaction P (IP)	0.17	0.91	0.75	0.36	0.59
Prospective design	97% (90 -100%)	95% (86 – 100%)	95% (86 – 100%)	89% (79 – 100%)	8%(2 – 18%)
Retrospective design	81% (72 – 91%)	75% (65 – 85%)	76% (68 – 84%)	64% (51 – 76%)	4% (0 – 7%)
IP	**0.009**	**0.003**	**0.002**	**0.002**	0.4
Peri-transplant RT	88% (76 – 100%)	59% (46 –71%)	91% (81 – 100%)	79% (66 – 91%)	1% (0 – 6%)
Salvage RT only	85% (76 – 93%)	77% (66 – 89%)	79% (69 – 90%)	71% (59 – 83%)	5% (2 – 8%)
IP	0.66	**0.03**	0.12	0.33	0.21

Subgroup analysis (a) histological type (b) study design (c) received peri-transplant radiotherapy.
Abbreviations: OS: Overall Survival; PFS: Progression Free Survival; RT: Radiotherapy; PMBCL: Primary Mediastinal Lymphoma; DLBCL: Diffuse Large B Cell Lymphoma.

The strengths of our study are as follows. Firstly, we performed a comprehensive literature search and were able to identify 12 eligible studies including 387 patients [29]. Secondly, to our knowledge, we are the first to pool results of salvage RT in patients with r/r DLBCL, in the rituximab era. Thirdly, we had a well-defined inclusion criteria. Studies which did not specify outcomes of interest were excluded [30]. Lastly, we assessed the quality of the included studies using the Newcastle-Ottawa scoring system. The main limitation of our study is the lack of a control group (i.e. patients treated without salvage RT). As such, we are not able to compare the incremental gain from the addition of RT. Most of the studies included in our meta-analysis were retrospective single-arm cohort studies [31]. In addition, we relied on published data and did not have access to individual-level data [32]. We acknowledge that the definition of salvage and consolidation RT may have varied between studies, resulting in some degree of selection bias. Lastly, the stage at relapse was not well reported (localized relapse versus systemic relapse), which may make interpretation of data challenging [33].

In conclusion, we report encouraging results for patients with r/r DLBCL who have been treated with salvage RT in the rituximab era [34,35]. These results contribute to the body of evidence for the utility of RT in this clinical situation where a multitude of treatment options exist and where novel therapeutics are evolving. Taking together the

known excellent local control rates of RT, the literature supporting improved outcome of achieving CR in the salvage setting for r/r DLBCL and the data generated from our meta-analysis, we highlight the therapeutic strategies and opportunities which exist to incorporate RT into prospective clinical trials. Factors such as the extent of r/r disease, eligibility for ASCT, sensitivity to salvage chemotherapy and the requirement for effective local control from local mass effect will be important to consider to optimally complement current and novel systemic regimens.

References

1. Chaganti S, Illidge T, Barrington S, Mckay P, Linton K, et al. (2016) Guidelines for the management of diffuse large B- cell lymphoma. British journal of haematology 174(1): 43-56.
2. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, et al. (2002) CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. New England Journal of Medicine 346(4): 235-242.
3. Coiffier B, Thieblemont C, Van Den Neste E, Lepeu G, Plantier I, et al. (2010) Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood 116(12): 2040-2045.
4. LYMPHOMAS AB-C. Review Series. Blood 2014; 577189.
5. Held G, Murawski N, Ziepert M, Fleckenstein J, Pöschel V, et al. (2014) Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. Journal of Clinical Oncology 32(11): 1112-1118.
6. Held G, Zeynalova S, Murawski N, Ziepert M, Kempf B, et al. (2013) Impact of rituximab and radiotherapy on outcome of patients with aggressive B-cell lymphoma and skeletal involvement. Journal of clinical oncology 31(32): 4115-4122.
7. Biswas T, Dhakal S, Chen R, Hyrien O, Bernstein S, et al. (2010) Involved field radiation after autologous stem cell transplant for diffuse large B-cell lymphoma in the rituximab era. International journal of radiation oncology biology physics 77(1): 79-85.
8. Gisselbrecht C, Schmitz N, Mounier N, Singh Gill D, Linch DC, et al. (2012) Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD_{20} (+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. Journal of Clinical Oncology 30(36): 4462-4469.
9. Ng AK, Yahalom J, Goda JS, Constine LS, Pinnix CC, et al. (2018) Role of radiation therapy in patients with relapsed/refractory diffuse large B-cell lymphoma: guidelines from the International Lymphoma Radiation Oncology Group. International Journal of Radiation Oncology Biology Physics 100(3): 652-669.
10. Bush R, Gospodarowicz M, Sturgeon J, Alison R (1977) Radiation therapy of localized non-Hodgkin's lymphoma. Cancer treatment reports 61(6): 1129-1136.
11. Persky DO, Unger JM, Spier CM, Stea B, LeBlanc M, et al. (2008) Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. Journal of clinical oncology 26(14): 2258-2263.
12. Blay J, Gomez F, Sebban C, Bachelot T, Biron P, et al. (1998) The International Prognostic Index correlates to survival in patients with aggressive lymphoma in relapse: analysis of the PARMA trial. Blood 92(10): 3562-3568.
13. Phan J, Mazloom A, Medeiros LJ, Zreik TG, Wogan C, et al. (2010) Benefit of Consolidative Radiation Therapy in Patients With Diffuse Large B-Cell Lymphoma Treated With R-CHOP Chemotherapy. Journal of Clinical Oncology 28(27): 4170-4176.
14. Illidge T, Specht L, Yahalom J, Aleman B, Berthelsen AK, et al. (2014) Modern radiation therapy for nodal non-Hodgkin lymphoma-target definition and dose guidelines from the International Lymphoma Radiation Oncology Group. International Journal of Radiation Oncology Biology Physics 89(1): 49-58.
15. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, et al. (2017) Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 130(16): 1800-1808.
16. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. European journal of epidemiology 25(9): 603-605.
17. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Controlled clinical trials 7(3): 177-188.
18. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. Bmj 327(7414): 557-560.
19. Lamy T, Damaj G, Soubeyran P, Gyan E, Cartron G, et al. (2018) R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma. Blood 131(2): 174- 181.
20. Bartlett NL, Wilson WH, Jung S-H, Hsi ED, Maurer MJ, et al. (2019) Dose-Adjusted EPOCH-R Compared With R-CHOP as Frontline Therapy for Diffuse Large B-Cell Lymphoma: Clinical Outcomes of the Phase III Intergroup Trial Alliance/CALGB 50303. Journal of Clinical Oncology 37(21): 1790-1799.
21. Dabaja BS, Hess K, Shihadeh F, Podoloff DA, Medeiros LJ, et al. (2014) Positron emission tomography/computed tomography findings during therapy predict outcome in patients with diffuse large B-cell lymphoma treated with chemotherapy alone but not in those who receive consolidation radiation. International journal of radiation oncology biology physics 89(2): 384-391.
22. Sauter CS, Matasar MJ, Meikle J, Schoder H, Ulaner GA, et al. (2015) Prognostic value of FDG-PET prior to autologous stem cell transplantation for relapsed and refractory diffuse large B-cell lymphoma. Blood 125(16): 2579-2581.
23. Wendland MM, Smith DC, Boucher KM, Asch JD, Pulsipher MA, et al. (2007) The impact of involved field radiation therapy in the treatment of relapsed or refractory non-Hodgkin lymphoma with high-dose chemotherapy followed by hematopoietic progenitor cell transplant. American journal of clinical oncology 30(2): 156-162.
24. Friedberg JW, Neuberg D, Monson J, Jallow H, Nadler LM, et al. (2001) The impact of external beam radiation therapy prior to autologous bone marrow transplantation in patients with non-Hodgkin's lymphoma. Biology of Blood and Marrow Transplantation 7(8): 446-453.
25. Gisselbrecht C, Van Den Neste E (2018) How I manage patients with relapsed/refractory diffuse large B cell lymphoma. British journal of haematology 182(5): 633-643.
26. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, et al. (2017) Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. New England Journal of Medicine 377: 2531-2544.
27. LaRiviere M, Wright C, Arscott W, Miller D, Weber E, et al. (2019) Induction Radiation Prior to Commercial Chimeric Antigen Receptor T-Cell Therapy for Relapsed/Refractory Non-Hodgkin Lymphoma. International Journal of Radiation Oncology Biology Physics 105(1): S66.
28. Broccoli A, Casadei B, Stefoni V, Pellegrini C, Quirini F, et al. (2017) The treatment of primary mediastinal large B-cell lymphoma: a two decades monocentric experience with 98 patients. BMC cancer 17(1): 276.
29. Chan EHL, Koh LP, Lee J, De Mel S, Jeyasekharan A, et al. (2019) Real world experience of R-CHOP with or without consolidative radiotherapy vs DA-EPOCH-R in the first-line treatment of primary mediastinal B-cell lymphoma. Cancer medicine 8(10): 4626-4632.
30. Chin V, Fulham M, Hertzberg M, Jackson M, Lindeman R, et al. (2018) Impact of salvage treatment modalities in patients with positive FDG-PET/CT after R-CHOP chemotherapy for aggressive B-cell non-Hodgkin lymphoma. Journal of medical imaging and radiation oncology 62(3):432-439.

31. Dorth JA, Chino JP, Prosnitz LR, Diehl LF, Beaven AW, et al. (2011) The impact of radiation therapy in patients with diffuse large B-cell lymphoma with positive post-chemotherapy FDG-PET or gallium-67 scans. Annals of oncology 22(2): 405-410.

32. Grignano E, Laurent J, Deau B, Burroni B, Bouscary D, et al. (2018) The role of radiotherapy as salvage and/or consolidation treatment in relapsed/refractory and high-risk diffuse large B-cell lymphoma. European Journal of Haematology 101(2): 150-159.

33. Hoppe BS, Moskowitz CH, Zhang Z, Maragulia JC, Rice RD, et al. (2009) The role of FDG-PET imaging and involved field radiotherapy in relapsed or refractory diffuse large B-cell lymphoma. Bone marrow transplantation 43(12):941-948.

34. Sert F, Kamer S, Saydam G, Anacak Y (2018) Role of consolidative radiation therapy for patients with mediastinal diffuse large B-cell lymphoma in the rituximab era. Journal of Cancer Research and Therapeutics 14(6): 1397-1402.

35. Holzhauser E, Berlin M, Wollschlager D, Bezold T, Mayer A, et al. (2017) Patterns of failure of diffuse large B-cell lymphoma patients after involved site radiotherapy. Strahlentherapie Onkologie 193(12): 1014-1023.