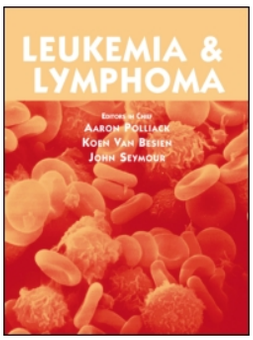

Leukemia & Lymphoma

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ilal20

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To cite this article: Karine A. Al Feghali, Penny Fang, Maria Gule-Monroe, Sarah Milgrom, Joseph D. Khoury, Jillian R. Gunther, Tommy Sheu, Ranjit Nair, Sairah Ahmed, Raphael Steiner, Paolo Strati, Elizabeth J. Shpall, Yago L. Nieto, Chitra Hosing, Loretta J. Nastoupil, Jason R. Westin, Sattva S. Neelapu, Nathan Fowler, Christopher Flowers, Chelsea C. Pinnix & Bouthaina S. Dabaja (2021): Prognostic value of disease distribution in secondary central nervous system diffuse large B cell lymphoma treated with radiation therapy, Leukemia & Lymphoma, DOI: 10.1080/10428194.2021.1919656

To link to this article: https://doi.org/10.1080/10428194.2021.1919656

LEUKEMIA & LYMPHOMA
https://doi.org/10.1080/10428194.2021.1919656

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ORIGINAL ARTICLE

Prognostic value of disease distribution in secondary central nervous system diffuse large B cell lymphoma treated with radiation therapy

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ABSTRACT

This study aimed to assess the prognostic value of baseline disease distribution for patients with the secondary central nervous system (CNS) diffuse large B-cell lymphoma (DLBCL) treated with chemotherapy and radiation (RT). 44 patients with secondary CNS DLBCL were reviewed. Twenty patients had leptomeningeal disease (LMD), and 24 had localized/targetable disease (LTD). Of 8 patients who received stem cell transplantation (SCT) after RT, 6 had LTD with a complete or partial response after RT. Median time to CNS relapse after RT was 10.1 months; 3/24 patients with LTD and 5/15 with LMD had CNS relapse. The median overall survival (OS) was 8 and 20 months for patients with LMD and LTD, respectively ($p = 0.20$). On multivariable analysis, LTD, receipt of SCT, and response after RT were associated with better OS and CNS-disease-free survival. Patients with localized secondary CNS DLBCL may benefit from RT serving as a bridge to SCT.

ARTICLE HISTORY
Received 2 October 2020
Revised 10 March 2021
Accepted 12 April 2021

KEYWORDS
Diffuse large B-cell lymphoma; central nervous system lymphoma; radiation therapy; stem cell transplantation; salvage therapy

Introduction

Despite improvements in survival of patients with diffuse large B-cell lymphoma (DLBCL) in the rituximab era, relapse in the central nervous system (CNS), albeit rare, still represents a considerable challenge to clinicians. The incidence of CNS involvement at diagnosis or CNS relapse ranges from 2 to 6% in unselected groups of DLBCL patients treated with rituximab [1–4]. Independent risk factors for CNS relapse include more than one site of extranodal involvement and increased lactate dehydrogenase levels [5]. In the current era, the prognosis of patients with secondary CNS DLBCL remains dismal with a median overall survival of around 2 months [6].

Successful treatment of secondary CNS DLBCL requires the eradication of both disease in the CNS and systemic disease and has entailed strategies including systemic and intrathecal chemotherapy and consolidation with autologous or allogeneic stem cell transplant (SCT). Achieving CNS disease remission prior to SCT is critical for achieving extended disease remission [7]. Radiation therapy (RT) has been identified as a potentially effective salvage strategy for secondary CNS lymphoma [8]. However, it is unclear which cohorts of patients may derive the most benefit from radiation compared to other treatments, and whether there are underlying factors such as CNS disease distribution, pathology or patient characteristics that may identify patients who are most likely to successfully respond and be bridged to consolidation with stem cell transplant or other therapies.

Improving the selection and sequencing of treatments for patients with secondary CNS DLBCL is of utmost importance. With the improvement in the survival of patients with relapsed/refractory DLBCL with newer therapies including chimeric antigen receptor

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Supplemental data for this article can be accessed here.

(CAR-T) cell therapy [9], the risk of relapse in sites that are not addressed by systemic chemotherapy may increase. Therefore, CNS-directed therapy such as radiation may be of increasing importance.

In this retrospective study, we aimed to identify factors associated with prognosis for patients with secondary CNS DLBCL treated with chemotherapy (CT) and radiation therapy in order to understand which patients may derive the most benefit from this approach. We focused specifically on baseline CNS disease distribution, categorized as localized/targetable disease (LTD) and leptomeningeal disease (LMD).

Materials and methods

Patients

This single-institution retrospective study was conducted after approval by the institutional review board. The charts of 44 patients with CNS involvement secondary to systemic DLBCL who were treated with CNS-directed RT between 2006 and 2016 were reviewed. Patients were grouped into 2 cohorts (LTD and LMD) based on disease location on initial imaging, all assessed and reviewed by a neuro-radiologist (MGM) for the purpose of this study. Patients with both LTD and LMD were categorized as LMD. LTD was defined as any set of lesions that could be encompassed in a radiation field that would not require a whole-brain field.

Additionally, an experienced pathologist specialized in hematopathology reviewed the slides from the initial tissue diagnosis and reported on the presence of high-grade features (including starry sky pattern, necrosis, increased mitotic/apoptotic features) and low-grade B cell features (as their presence could represent secondary DLBCL following Richter-type transformation).

A complete response (CR) was defined as resolution of gadolinium-enhancing abnormalities; partial response (PR), as 50% reduction; stable disease (SD), as $<$50% reduction to $<$25% growth; and progressive disease (PD), as $\geq$25% growth or appearance of any new lesion [10,11]. The product of the axial bidirectional diameters (anteroposterior $\times$ transverse) was used for response assessments [11]. Measurements were obtained from axial postcontrast T1 images.

Endpoints and statistical analyses

Descriptive statistics were used to analyze the distribution of the sample by sex, ethnicity, age, clinical data, treatment modality, fractionation schemes, and functional outcomes. Demographic, clinicopathologic and treatment-related factors were examined for association with outcomes. The Kaplan–Meier product limit method was used to calculate survival endpoints [12], and log-rank tests were used to compare the survival distributions of two samples. All survival endpoints were calculated from the date of radiological diagnosis of CNS involvement or relapse until the date of the event. CNS disease-specific survival (CNS-DFS) was defined as CNS progression or death as events (and all others censored); and overall survival (OS) as death from any cause as an event (and all others censored). Both univariate and multivariate Cox proportional hazards analyses were used to investigate potential correlations between patient- and treatment-related factors (including age at diagnosis, gender, Eastern Cooperative Oncology (ECOG) performance status at the time of CNS relapse, CNS disease location, high-grade and low-grade features on pathology, molecular subtype) and outcomes (disease control and survival endpoints). Univariate Cox proportional hazards analysis was also used to stratify CNS-DFS, and OS by disease location (LTD versus LMD), as well as by receipt of stem cell transplantation. JMP 14 Pro statistical software (SAS Institute, Cary, NC) was used for data analysis, and statistical significance was determined by using a prespecified α of 0.05.

Results

Patients

The study group consisted of 44 patients (68% men and 32% women). Median age at the time of initial diagnosis of DLBCL was 55 years (range 23–83). Three patients had CNS involvement at presentation and 41 had CNS disease at relapse; 20 patients had LMD, and 24 had LTD. An example of a patient with LTD and his/her radiation treatment plan is pictured in Figure 1. An example of a patient with LMD is depicted in Figure 2. Fifteen patients (34%) had active extra-cranial disease at the time of their diagnosis with CNS involvement, and 14 (32%) had active extra-cranial disease at the time of RT. 34 patients (77%) had neurological symptoms prior to initiation of RT. The neoplastic cells expressed immunophenotypic features consistent with germinal center B-cell origin in 16/44 (36%) of cases; 2 patients had primary cutaneous DLBCL, leg-type. Distinct pathologic features in some included low-grade B-cell components in 7 (16%) and high-grade features (e.g. starry sky pattern) in 14 (32%) patients, with no significant correlation with CNS disease distribution. Patient and disease characteristics are outlined in Table 1.

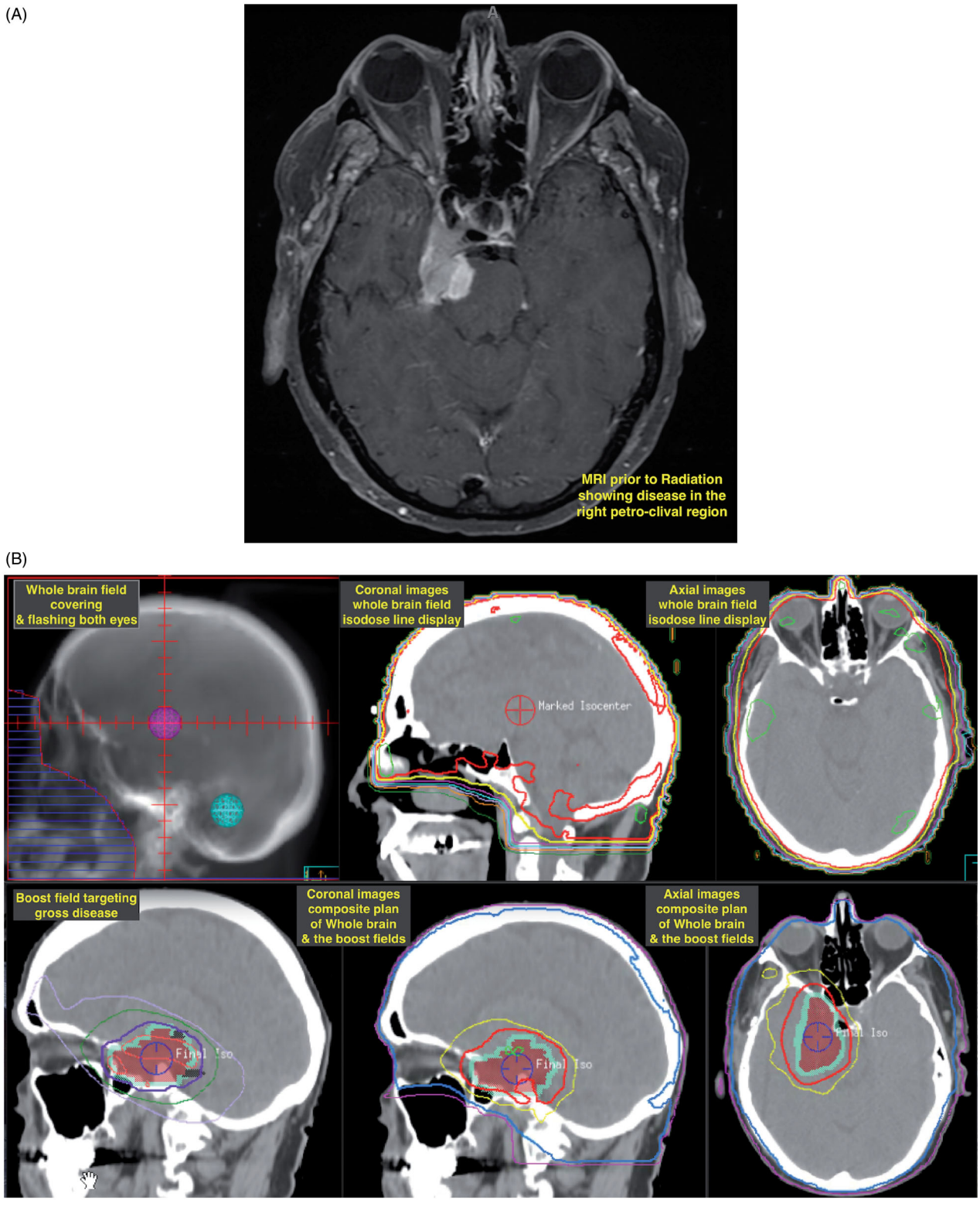


Figure 1. Example of localized/targetable disease in the setting of secondary central nervous system diffuse large B cell lymphoma (A), and radiation therapy plan (B) to treat this lesion. The eyes were included in the radiation fields because of suspicion of intraocular involvement.

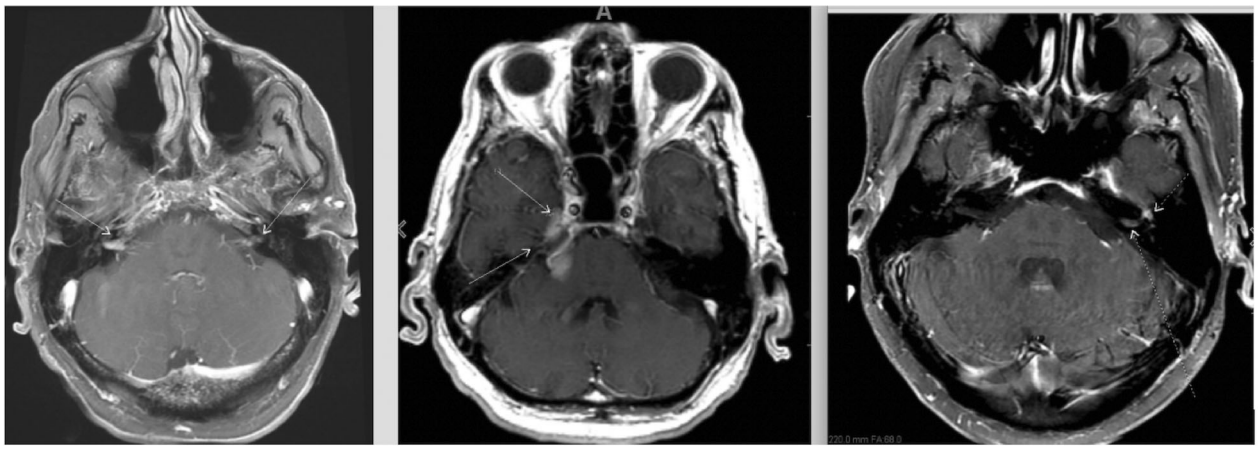


Figure 2. Example of leptomeningeal disease in the setting of secondary central nervous system diffuse large B cell lymphoma.

Treatment

The majority of patients (75%) received R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) as front-line CT, and 31 patients (70%) were given CNS-directed CT prior to RT. In 30 of these, the regimen included high-dose methotrexate. A median of 1 line of chemotherapy (range: 1–4 lines) was administered to patients with CNS relapse prior to RT. Only 2 patients had CR (and therefore no measurable disease) at the time of RT, and were treated as consolidation. Whole-brain RT was given in 43 patients, and the craniospinal axis was treated in 1, with a median RT dose of 30 Gy (range 18–31 Gy). 13/44 received a boost to the gross disease with a median of 9 Gy (range 5–20 Gy). The median final RT dose was 30 Gy (range 18–45). Of 8 patients who eventually received stem cell transplantation (SCT), 6 had LTD, and all had a complete or partial response after RT. Treatment characteristics are summarized in Table 2.

Oncologic outcomes and survival

CNS relapses and CNS-DFS

At a median follow-up of 12.3 months for the entire cohort (range 0.9–103.3), median time to CNS relapse after RT was 10.1 months (interquartile range; 6.4–132.6 months); 3/24 (13%) patients with LTD and 5/15 (33%) with LMD had CNS relapse. 7 patients relapsed in the CNS outside the radiation fields (spine, CSF and/or development of LMD). 1-year and 2-year CNS-DFS rates for the entire cohort were 50% and 28%, respectively. 1-year CNS-DFS rates for patients with LTD and LMD were 60% and 38%, respectively, and 2-year CNS-DFS were 36% and 17%, respectively ($p = 0.17$) (Figure 3). 1-year CNS-DFS rates for patients who received SCT after RT were 88% versus 41% for patients who did not, and 2-year CNS-DFS rates were 75% and 14%, respectively ($p = 0.001$) (Figure 4). Univariate analyses of factors associated with CNS-DFS are depicted in Supplementary Table 1. While the use of CNS-directed CT prior to RT was not associated with better disease outcomes, when considering patients in the top surviving quartile, 73% had LTD, and 55% transitioned to SCT after response to RT. Increased radiation dose was not associated with better CNS-DFS.

Factors significantly associated with improved CNS-DFS on MVA were the extent of radiographic response after RT ($p < 0.001$), localized/targetable disease (versus LMD) ($p = 0.007$), receipt of SCT after RT ($p = 0.014$), better ECOG performance status at diagnosis of CNS disease ($p = 0.031$), and the absence of active systemic disease at the time of CNS relapse ($p = 0.036$) (Supplementary Table 2).

Overall survival

At a median follow up of 12.3 months for the entire cohort (range 0.9–103.3), 30 patients had died. The median survival for the entire cohort was 12.8 months. The median overall survival was 8 months, and 20 months for patients with LMD and LTD, respectively ($p = 0.20$). 1-year and 2-year OS for the entire cohort were 55% and 31%, respectively. 1-year OS rates for patients with LTD and LMD were 69% and 38%, respectively, and 2-year OS rates were 39% and 20%, respectively ($p = 0.19$). 1-year OS rates for patients who received SCT after RT were 100% versus 44% for patients who did not, and 2-year OS rates were 100% and 14%, respectively ($p < 0.001$). Univariate analysis of factors associated with OS is depicted in Supplementary Table 3. Radiation dose was not associated with OS.

Table 1. Patient and disease characteristics.

Characteristic	*N* (%)
Sex	
Male	30 (68)
Female	14 (32)
Age	
Median (range), y	55 (23,83)
DLBCL subtype	
GCB type	16 (36)
Non-GCB type	13 (30)[a]
Unknown	15 (34)
Stage at initial diagnosis	
I	7 (16)
II	7 (16)
III	6 (14)
IV	24 (54)
Number of extranodal site at diagnosis	
0	10 (23)
1–2	18 (41)
>2	16 (36)
Involvement of high-risk extranodal sites	
Renal or adrenal	8 (18)
Breast	5 (11)
Testicle	2 (5)
IPI at initial diagnosis	
0–1	2 (10)
2–3	8 (40)
4–5	10 (50)
High-grade features on pathology (including starry sky)	
Present	14 (33)
Absent	28 (67)
Low-grade B cell component	
Present	7 (17)
Absent	35 (83)
Time to diagnosis of CNS relapse	
<1 year	25 (57)
≥1 year	19 (43)
ECOG Performance status at time of CNS relapse	
1	7 (16)
2	21 (48)
3	16 (36)
Radiographic findings at time of CNS DLBCL detection	
Localized/Targetable	24 (55)
Leptomeningeal disease	20 (45)

DLBCL: diffuse large B cell lymphoma; GCB: germinal center B-cell-like; IPI: international prognostic index; ECOG: Eastern Cooperative Oncology Group; CNS: central nervous system.
[a]Including 2 patients with primary cutaneous DLBCL, leg type.

Table 2. Treatment characteristics.

Characteristic	*N* (%)
CNS-directed chemotherapy prior to CNS relapse	
Yes	14 (32)
No	30 (68)
Type of	
Salvage CNS-directed chemotherapy after CNS relapse and before RT	
Yes	31 (70)
No	13 (30)
Best response to salvage CNS-directed chemotherapy prior to RT	
CR/PR	10 (33)
SD/PD	20 (67)
Stem cell transplantation after RT	
Yes	8 (18)
No	36 (82)

CNS: central nervous system; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease.

Factors significantly associated with a better OS on MVA were the receipt of SCT after RT ($p < 0.001$), the extent of radiographic response after RT (complete response (CR)/partial response (PR) versus stable disease (SD)) ($p < 0.001$), better ECOG performance status at diagnosis of CNS disease ($p = 0.004$), presence of low-grade B cell component ($p = 0.004$), the absence of active extracranial disease at the time of CNS relapse ($p = 0.010$), CR/PR to salvage CNS-directed chemotherapy prior to radiation therapy (versus SD/PD) ($p = 0.010$), and localized/targetable disease (versus LMD) ($p = 0.030$) (Supplementary Table 4).

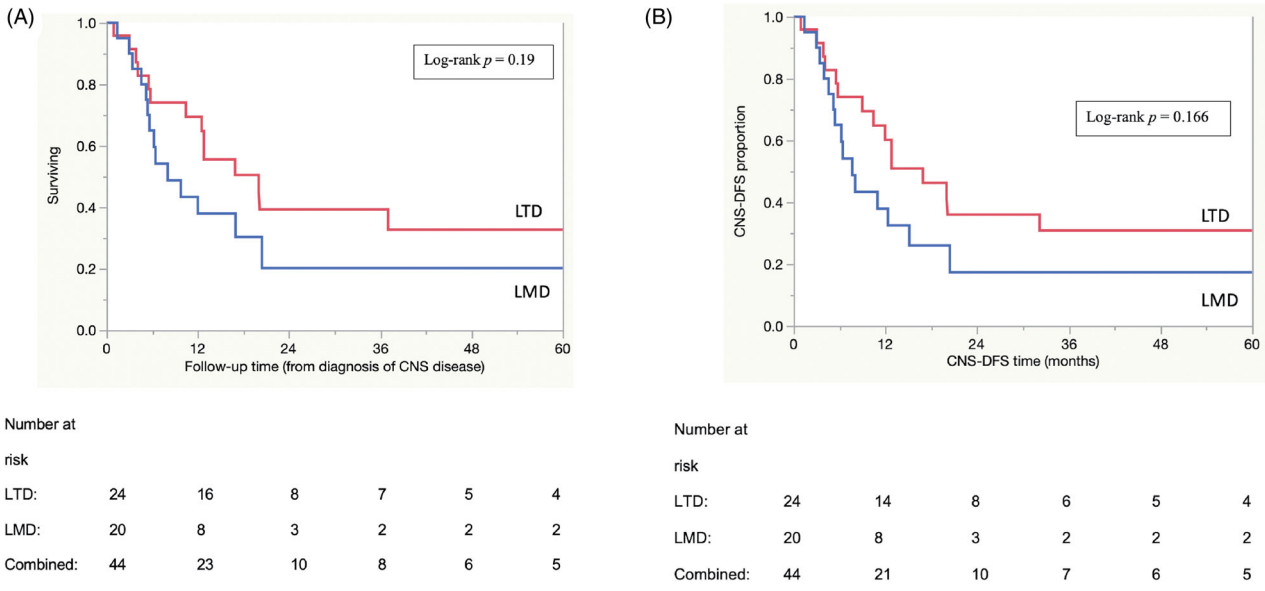
LMD versus LTD

Given the difference in outcomes of patients with LMD versus LTD, we explored whether any other prognostically significant factors were unevenly distributed between these two groups. When comparing patients with LMD to those with LTD, we found no significant differences in molecular subtype, presence of high-grade features or low-grade B cell component on pathology, presence of active extracranial disease, extent of radiographic response after salvage CNS-directed chemotherapy, and RT dose/use of an RT boost (Supplementary Table 5).

Discussion

This study of patients with secondary CNS DLBCL treated with chemotherapy and radiotherapy revealed that patients with LTD achieved improved disease outcomes compared to those with LMD. The patients in our cohort who experienced the best oncologic and survival outcomes were those who underwent SCT after RT. These findings suggest that patients who underwent RT and were subsequently able to undergo SCT had better CNS disease control than those who were not able to undergo SCT, particularly in the setting of LTD disease.

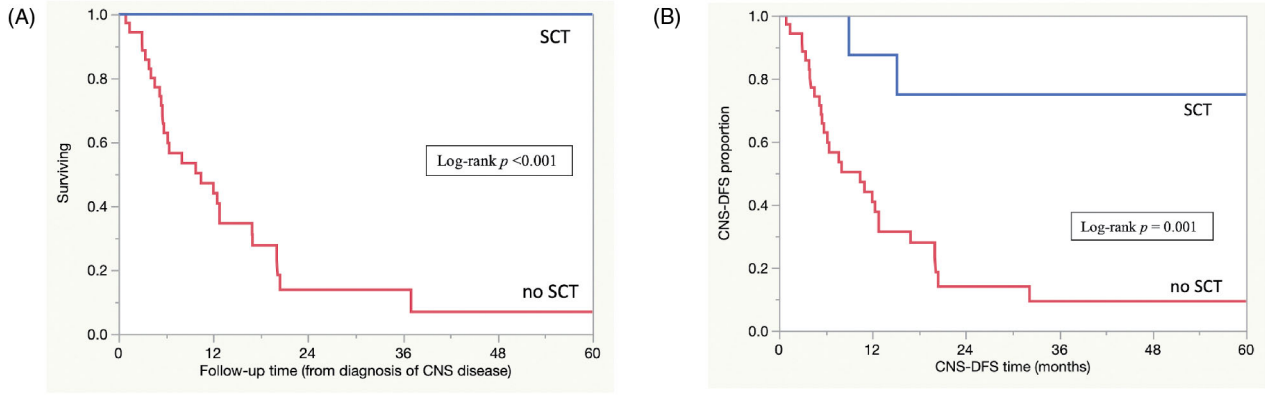
Our prior study of radiation as salvage therapy for patients with secondary CNS lymphoma has noted that progression after RT involved the CNS in only a minority of cases and systemic sites outside the CNS in the majority [8]. This was in contrast to outcomes in cohorts of patients treated with high dose CT and SCT without RT, such as in a study in which patients were treated with methotrexate, CT, and SCT, in which the vast majority of patients relapsed in the CNS [13]. This finding suggested that there is indeed a potential benefit of CNS-directed local therapy with radiation that may not be as durable as with IT or systemic therapies.



Number at risk						
LTD:	24	16	8	7	5	4
LMD:	20	8	3	2	2	2
Combined:	44	23	10	8	6	5

Number at risk						
LTD:	24	14	8	6	5	4
LMD:	20	8	3	2	2	2
Combined:	44	21	10	7	6	5

Figure 3. Kaplan Meier curves showing (A) Overall survival and (B) Central nervous system-disease free survival by disease location through 60 months. LTD: localized/targetable disease; LMD: leptomeningeal disease; CNS-DFS: Central nervous system-disease free survival.



Number at risk						
SCT:	8	8	7	6	5	4
No SCT:	36	15	4	3	2	2
Combined:	44	23	10	8	6	5

Number at risk						
SCT:	8	8	7	6	5	4
No SCT:	36	14	4	2	2	2
Combined:	44	21	10	7	6	5

Figure 4. Kaplan Meier curves showing (A) Overall survival and (B) Central nervous system-disease free survival by receipt of stem cell transplantation through 60 months. SCT: stem cell transplantation; CNS-DFS: Central nervous system-disease free survival.

However, this study identified, that among patients with secondary CNS lymphoma treated with radiation, those with LTD disease distribution seem to be particularly good candidates for this treatment approach with the best treatment outcomes. There are many potential reasons for this: LTD may represent overall a lower CNS disease burden relative to LMD, which may be more amenable to control with a CT and RT strategy. It may also be postulated that LMD is associated with inherently worse disease pathology compared to LTD. However, our analysis does not support this, and we did not find any significant differences with regards to pathologic features between LTD and LMD. Also, while conceptually it may be more difficult to

treat LMD with the same radiation dose as LTD which could affect outcome, we did not find any association between radiation dose and disease outcome. One caveat is that, in this study, only one patient received craniospinal RT, which more comprehensively targets the entire central CNS axis including the brain and spine. Since some of the patients in our study relapsed in the CNS outside the RT fields, it is possible that with a more aggressive and comprehensive CSI approach, even in patients with limited LMD, additional patients may have achieved durable remission although this has to be weighed with increased CNS toxicity risk, and this needs to be studied subsequently.

The fact that some patients presented with secondary CNS disease without active systemic disease might indicate that the CNS disease was not adequately addressed with the previous systemic chemotherapy. Therefore, this presents an opportunity for CNS-directed therapy, in particular, radiation therapy that could constitute an effective modality to control the disease and permit further definitive therapies, for instance transplant. Patients in this study who achieved superior radiographic response to radiation and were able to proceed to SCT had the best outcomes. A previous publication supports similar prolonged disease-free survival benefit from SCT in patients with CNS disease [14], An alternative explanation to the improved outcomes in those who received transplant is that transplant was a surrogate for responding to the CNS directed therapy. The best outcome after SCT is in patients who have achieved minimal to no residual disease with prior therapies [7]. While this study was conducted prior to the CAR-T cell era, the same principles potentially apply to patients who are potential candidates for CAR-T cell therapy. Those with CNS disease that is otherwise difficult to treat with IT and systemic therapies may benefit from RT that effectively bridges them to CAR-T cell therapy. The effort to study and define which patients with CNS disease benefit from RT bridging to CAR-T is ongoing at our institution and others.

In terms of optimal radiation dose and technique, it is crucial to aim to achieve the best therapeutic ratio by ensuring a low risk of long-term toxicity, particularly neurotoxicity. Although in this study, median radiation dose was 30 Gy, we currently use an approach of giving a lower dose of radiation such as 23.4–24Gy to the whole brain, and boosting sites of gross disease to approximately 40–45Gy [15].

We acknowledge that this study has inherent limitations related to its retrospective nature. We were not able to adequately study the correlation between molecular subtypes and outcomes as we were originally planning as this information was missing for many patients. The number of patients is also relatively small, and a larger cohort of patients is needed to validate our findings.

In summary, patients with LTD had improved oncologic outcomes and survival compared to those with LMD. Patients with localized secondary CNS DLBCL may therefore derive benefit from RT that serves as a bridge to SCT.

Disclosure statement

CCP has received research funding from Merck. LJN has received honorarium from Bayer, Celgene, Gamida Cell, Genentech, GILEAD/KITE, Janssen, Novartis, TG Therapeutics. LJN has received research funding from Celgene, Genentech, Janssen, Karus Therapeutics, LAM Therapeutics, and TG Therapeutics.

SSN has received research support from Kite/Gilead, Cellectis, Poseida, Merck, Acerta, Karus, BMS, Unum Therapeutics, Allogene, and Precision Biosciences; served as consultant and advisory board member for Kite/Gilead, Celgene, Novartis, Unum Therapeutics, Pfizer, Merck, Precision Biosciences, Cell Medica, Incyte, Allogene, Calibr, and Legend Biotech; has patents related to cell therapy.

Funding

This work was supported by Cancer Center Support Grant [CA016672].

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