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TO THE EDITOR:

Salvage radiotherapy is associated with durable response for a subset of patients with limited-stage refractory DLBCL

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Approximately one third of patients with diffuse large B-cell lymphoma (DLBCL) experience relapsed or refractory disease, portending a poor prognosis. Approximately two thirds of these are of advanced age or with comorbidities precluding salvage chemotherapy and autograft. Such patients may be offered palliative chemotherapy or radiotherapy, investigational agents, or chimeric antigen receptor T-cell therapy on clinical trial or, potentially, salvage radiotherapy with curative intent in the setting of single-site progression. Freeman et al recently reported their outcomes using radiotherapy consolidation for patients treated with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) chemoimmunotherapy for DLBCL, according to end-of-induction positron emission tomography (PET) response.[1] The article and accompanying commentary addressed the controversy around consolidative radiotherapy in a nonprogressive PET-positive response; however, the absence of repeat biopsy of PET-positive sites raised the question about what proportion of patients had residual viable lymphoma and whether salvage radiotherapy with curative intent is feasible in patients unsuitable for further intensification and stem cell transplantation.[2]

There remains a paucity of evidence for curative-intent radiotherapy in relapsed/refractory DLBCL (rrDLBCL), with no randomized clinical trials or large series reported in the literature, with the exception of those by Freeman et al and related database/registry studies that have empirically applied radiotherapy without biopsy-proven evidence of persistent viable lymphoma.[1,3,4] We conducted a study to assess the outcomes of patients treated with salvage radiotherapy for limited-stage rrDLBCL at Monash Health to determine its utility and inform future treatment algorithms.

DLBCL cases (867 patients) diagnosed per World Health Organization criteria at Monash Health between 1996 and 2019 were analyzed. Adult patients with rrDLBCL (including transformed indolent lymphoma) treated with salvage radiotherapy alone with curative intent were included in the study. Patients with inadequate clinical information or follow-up data available or those in whom radiotherapy was administered as consolidation or clearly palliative intent were excluded. The study was reviewed by the institutional Human Research Ethics Committee and approved as a Quality Assurance activity. It was conducted in accordance with the Declaration of Helsinki.

From January of 1996 to December of 2019, 32 patients were identified, but 14 were excluded for the following reasons: received radiotherapy for clearly palliative intent (n = 7), central nervous system relapse (n = 5), consolidation (n = 1), and prior indolent lymphoma (n = 1). Of 18 eligible patients, 14 were refractory to recent chemoimmunotherapy (including 1 transformation of follicular lymphoma on therapy) and 4 were relapsed after a complete remission interval following the most recent systemic therapy. Histological diagnoses (according to the Hans algorithm) included germinal center DLBCL (n = 6), activated B-cell DLBCL (n = 5), transformed follicular lymphoma (n = 4), T-cell/histiocyte-rich large B-cell lymphoma (n = 1), high grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangement (n = 1), and Richter's transformation of chronic lymphocytic leukemia to DLBCL (n = 1). For the population, median stage at DLBCL diagnosis was 4 (range, 1-4), with 5 of 18 patients (27.8%) having limited stage 1-2 disease. Median revised International Prognostic Index (R-IPI) was 3 (range, 0-5) with 13 patients having an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2. Initial therapy for DLBCL was R-CHOP/CHOP-like (6 cycles, n = 11; 3 cycles, n = 2), R-EPOCH

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Data sharing requests should be sent to Gareth P. Gregory (gareth.gregory@monash.edu).

The full-text version of this article contains a data supplement.

Table 1. Patient, disease, treatment, and response demographics for the patient cohort

No.	Age at Dx, y; sex	Pathology	Treatment and response	PET DS prior to RT	RT dose, Gy	Progression field (RT)
1	62; M	DLBCL: GCB subtype	R-CHOP ×6 > PR > **salvage RT to head/neck***	4	45	Out
2	75; M	DLBCL: GCB subtype	R-CHOP ×6 > PR > **salvage RT to mediastinum†**	5	50	Ongoing remission
3	59; F	DLBCL: transformed FL	Prior multiply-relapsed FL including CHOP ×6 > transformation DLBCL > salvage chemotherapy and autograft > PD > EPOCH ×1 > CR > PD > **salvage RT to S1 nerve root***	5	10 (planned 44)	In/out
4	76; M	DLBCL: GCB subtype	R-CHOP ×6 > PD > **salvage RT to cecal mass†**	5	45	In/out
5	74; F	DLBCL: transformed FL	Prior FL CHOP ×6 > CR > transformation DLBCL > R-CEOP ×6 > PD > **salvage RT to abdominal node‡**	5	30.6	Ongoing remission
6	70; M	DLBCL: ABC subtype + double expressor	R-EPOCH ×6 > PD > **salvage RT to maxillary progression†**	5	32.4 (planned 36)	Out
7	74; M	DLBCL: ABC subtype	R-CHOP ×6 > PD > **salvage RT to axilla†**	5	44	Out
8	42; M	DLBCL: GCB subtype + double expressor	R-CHOP ×3 > PD > **salvage RT to inguinal node†**	5	50	In/out
9	78; F	DLBCL: GCB subtype	R-CHOP ×6 > CR > PD > **salvage RT to mediastinum‡**	5	40	Ongoing remission
10	53; M	HGBL with *MYC* and *BCL2* and/or *BCL6R*	R-EPOCH ×6 > PR > **salvage RT to paratracheal node‡**	4	40	Ongoing remission
11	70; M	DLBCL: transformed FL	Prior FL > R-bendamustine > PR > PD transformation to DLBCL > **salvage RT to parotid node†**	5	50.4	Ongoing remission
12	67; F	DLBCL: T cell/histiocyte rich	R-CHOP ×6 > CR > PD > GemOx > CR > PD > **salvage RT to C7 vertebra***	5	40	Out
13	48; M	DLBCL: transformed FL	Prior FL > R-CHOP ×6 > PD transformation to DLBCL parotid > R-IVAC ×2 > PD > **salvage RT to parotid†**	5	40	Out (FL)
14	83; M	DLBCL: transformed CLL	Attenuated R-CHOP ×3 > PR > **salvage RT to groin***	4	30	Ongoing remission
15	71; F	DLBCL: GCB subtype	R-CHOP ×6 > PD > **salvage RT to retroperitoneum†**	5	45	Ongoing remission
16	69; M	DLBCL: ABC subtype	R-CHOP ×6 > CR > PD > **salvage RT to submandibular node†**	5	46	Out
17	76; F	DLBCL: ABC subtype	R-CHOP ×6 > PD (spleen) > splenectomy† > splenic bed progression > **salvage RT to splenic bed**	5	40	In/out
18	65; M	DLBCL: ABC subtype	R-CHOP ×6 > PD > **salvage RT to stomach†**	5	50	Out

Abbreviated treatment course is provided; full patient journeys are provided in supplemental Table 1. Progression field denotes whether patients progressed in or out of field of RT. Bold text denotes timing and site of radiotherapy.

CLL, chronic lymphocytic leukemia; CR, complete response; Dx, diagnosis; DS, Deauville score; EPOCH, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin; F, female; FL, follicular lymphoma; GemOx, gemcitabine, oxaliplatin; HGBL, high grade B-cell lymphoma; M, male; PD, progressive disease; PR, partial response; R, rituximab; RT, radiotherapy; R-CEOP, rituximab, cyclophosphamide, etoposide, vincristine, prednisolone; R-IVAC, rituximab, ifosfamide, etoposide, cytarabine.

*Biopsy was not performed, but imaging was highly suspicious for disease.

†Biopsy-proven progression.

‡Biopsy was inconclusive.

(rituximab, etoposide, prednisolone, vincristine, cyclophosphamide, doxorubicin) (n = 2), or IVAC (ifosfamide, etoposide, cytarabine) (n = 2; both had received prior R-/obinutuzumab-CHOP for follicular lymphoma), and 1 patient was treatment naive for DLBCL, having transformed from follicular lymphoma while on rituximab-bendamustine therapy.

For the study population, median age at radiotherapy commencement was 71 years (range, 42-83). Of the 18 patients, 11 had biopsy-proven refractory/relapsed disease, 3 patients had inconclusive biopsy with high suspicion of active disease on imaging, and the remaining 4 patients were treated on the basis of high clinical suspicion from PET imaging with sites not amenable to biopsy. Patient histologies and treatment journeys are shown in Table 1 and supplemental Table 1.

The median radiotherapy dose administered was 42 Gy (range, 10-50). Radiotherapy technique was involved-site radiotherapy using 3-dimensional conformal radiotherapy, volumetric modulated arc therapy, or intensity-modulated radiation therapy, with the latter 2 methods used for more recent patients, especially when tumors were adjacent to dose-limiting normal tissues. Most patients were treated before International Lymphoma Radiation Oncology Group (ILROG) guidance was widely adopted.[5] Doses ≥50 Gy were

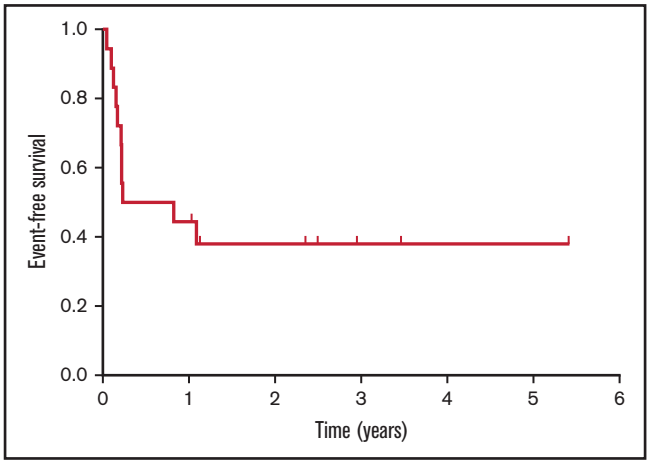

Figure 1. Event-free survival from radiotherapy commencement for the cohort of 18 patients.

used in selected cases based on anecdotal evidence of radioresistance in chemoimmunotherapy-resistant, refractory, or rapidly growing bulky aggressive lymphomas and the suggestion that, in refractory cases, the dose response curve may not be flat at >40 Gy. The general aim was to deliver ≥36 to 40 Gy to all sites of gross computed tomography–apparent and/or FDG-avid disease in 1.8 to 2 Gy-fractions, depending on tumor location and volume. Previous sites of involvement located adjacent to currently fluorodeoxyglucose-avid disease were also encompassed if dosimetric constraints for normal tissues could be met. Radiotherapy was terminated before completion if disease progression occurred locally or at other sites during the course, explaining why some patients received only low-dose radiotherapy.

After a median follow-up of 14 months (range, 1-64), 11 of 18 patients progressed (Figure 1) after a median of 2 months (range, 0-13). Seven patients (39%) remain in an ongoing remission without any progression events after a median follow-up of 29 months (range, 13-64). Notably, of these 7 patients, 3 had biopsy-proven unequivocal evidence of viable lymphoma, 2 had inconclusive attempted biopsies, and 2 had imaging sites not amenable to biopsy. Of the primary refractory subset of 14 patients, 6 (43%) remain free from progression with a median follow-up of 32 months (range, 12-64).

Subset analysis of patients who maintained a durable remission following radiotherapy and those who progressed was performed to identify predictors of durable response. The remission and progression groups were matched for baseline disease stage at the time of DLBCL diagnosis (median, 4; range, 1-4 in both groups), R-IPI (remission group: median, 3; range, 1-5 vs relapse group: median, 3; range 0-5), and ECOG PS (median favorable ECOG PS 0-2 in both groups) (supplemental Table 2).

An interesting observation is that, of the patients who were treated for relapsed DLBCL, only 1 of 4 is in an ongoing remission compared with 6 of 14 patients with primary refractory disease (supplemental Table 2). Although limited by the small number, one could hypothesize that the patients who were treated for relapsed disease may have appeared to be relapsing at an isolated site at the time of imaging but that most were already destined for progression elsewhere (possibly already at other sites below the sensitivity of PET detection), because their relapses predominantly occurred out of radiation field. The sum of products of dimensions was calculated for each subject, and there was no association observed between the volume of disease treated and the likelihood of long-term response (supplemental Table 2). However, of the 3 patients with a PET Deauville Score of 4 following the most recent line of therapy, 2 remain in ongoing remission following salvage radiotherapy, suggesting that patients who are responding to systemic therapy with single-site residual disease may derive benefit from this strategy without further salvage therapy (supplemental Table 2).

This small series supports the hypothesis that salvage radiotherapy to a solitary site of biopsy-proven rrDLBCL may achieve meaningful disease control for a subset of patients. This is of relevance in the context of the overall poor prognosis for patients with rrDLBCL, as evidenced recently by the SCHOLAR-1 retrospective study (n = 636 patients, overall response rate, 26%; complete remission, 7%, to next line of therapy) and the ZUMA-1 long-term follow-up study of axicabtagene ciloleucel (overall response rate, 83%; complete remission, 58%; median duration of response, 11.1 months).[6,7] Despite the inherent limitations of the small sample size, the lack of definitive biopsy for a subset of our patients, and the retrospective nature of the study, we conclude that salvage radiotherapy should be considered a treatment option for patients who are ineligible for salvage chemotherapy in cases of single-site rrDLBCL. These findings warrant further clinical investigation and validation in larger registry data sets.

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