

The Evolving Role of Radiation Therapy in DLBCL: From Early-Stage to Refractory Disease

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ABSTRACT

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma. Historically, radiation therapy (RT) served as the primary treatment modality for patients with localized disease. While still an option for select patients who are not candidates for systemic therapy, RT is currently used most frequently as a consolidation treatment after chemoimmunotherapy. Consolidation RT is most commonly recommended after an abbreviated course of systemic therapy in patients who have bulky disease or multiple risk factors, or in the setting of a partial response. Consolidation RT is also appropriate in some patients with advanced DLBCL, including those presenting with bulky disease (≥ 7.5 cm). While many patients achieve sustained remissions after first-line therapy, up to 50% of patients with DLBCL will eventually relapse. The most common salvage options include second-line chemotherapy followed by high-dose chemotherapy and autologous stem cell transplantation (ASCT) and chimeric antigen receptor (CAR) T-cell therapy. RT can be used in both settings to optimize clinical outcomes. This includes consolidation RT in patients with localized presentations or bulky disease in the setting of ASCT and bridging RT in select patients undergoing CAR T-cell therapy. RT is also a valuable modality in any patient with symptomatic disease requiring palliation.

PERSPECTIVE

Bradford S. Hoppe, MD, MPH; and Omran Saifi, MD, shares perspective on radiation therapy in DLBCL on [page 722](#)

Introduction

Several major advances have been incorporated into the management of diffuse large B-cell lymphoma (DLBCL) over the past 2 decades. PET-CT not only improves the accuracy of initial staging but also provides a means to more precisely assess response to therapy and provide risk-adapted treatment. The incorporation of rituximab into multiagent chemotherapy regimens has significantly improved survival in all stages of disease. Finally, chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of relapsed and refractory (R/R) disease.

One of the first modalities used to treat DLBCL was radiation therapy (RT).^{1,2} Historically, early-stage DLBCL was managed with RT alone, which successfully controlled about 40% to 45% of cases.³⁻⁵ RT subsequently transitioned to a consolidation modality after chemotherapy^{6,7} or chemoimmunotherapy.⁸ RT has always been a valuable palliative intervention to alleviate symptoms such as pain. The role of RT continues to evolve in the setting of improved systemic therapies and disease response assessment tools. This article will review the evolving role of RT in

DLBCL, from a consolidation modality in early-stage disease to a bridging modality prior to CAR T-cell therapy in refractory disease.

Consolidation RT: Early-Stage Disease Pre-Rituximab/PET-CT Era: Prospective Trials

Several randomized studies conducted before the use of rituximab or PET-CT evaluated whether RT provides benefit as a consolidation treatment after a full course of chemotherapy or whether RT might allow for fewer cycles of chemotherapy (**Table 1**).^{6,7,9} While now of historical significance, these influential studies shaped the management of DLBCL for many years and provide valuable insights that are still relevant today.

The primary objective of ECOG 1484 was to assess the role of consolidation RT if a complete response (CR) was achieved after a full course of chemotherapy.⁶ Patients were initially treated with 8 cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). If a CR was achieved by CT imaging, then patients either received consolidation RT (30 Gy) or were observed, depending upon prior randomization. All patients achieving only a partial response (PR) received a higher dose of RT (40 Gy). Notably, the ECOG study enrolled higher-risk patients (31% had disease bulk ≥ 10 cm; 68% had stage II disease). Among the patients achieving a CR, disease-free survival was significantly greater with consolidation RT (73% vs 56%; $P = .05$). Overall survival (OS), a secondary end point, also favored consolidation RT but was not statistically significant (82% vs 71%; $P = .24$). Local failure occurred in only 3 of 79 patients (4%) receiving RT.

The SWOG 8736 study explored a different question: Could RT replace (many) cycles of chemotherapy?⁷

Patients were randomized to 8 cycles of CHOP or 3 cycles of CHOP with consolidation RT (40-55 Gy). The SWOG study enrolled more favorable patients than the ECOG trial (68% had stage I; 29% had all gross disease resected at the time of diagnostic biopsy; patients with stage II bulky disease were not eligible). Perhaps unexpectedly, the SWOG study showed that abbreviated chemotherapy with consolidation RT improved both progression-free survival (PFS; 77% vs 64%; $P = .03$) and OS (82% vs 72%; $P = .02$) at 5 years compared with a full course of chemotherapy alone, and with less cardiac toxicity. However, there were more late systemic relapses with only 3 cycles of CHOP, such that PFS and OS curves merged by year 10.¹⁰

Finally, the Groupe d'Etudes des Lymphomes de l'Adulte (GELA) 93-4 study was designed to evaluate whether consolidation RT provides value in older patients without risk factors after 4 cycles of chemotherapy.⁹ Patients older than 60 years with no adverse prognostic factors per the International Prognostic Index (IPI) were randomly assigned to 4 cycles of CHOP or 4 cycles of CHOP with consolidation RT (40 Gy). This study showed no difference in event-free survival (EFS; 61% vs 64%; $P = .6$) or OS (72% vs 68%; $P = .5$) between the 2 arms.

Several lessons can be drawn from these heterogeneous studies conducted in the pre-rituximab/PET-CT era:

- Consolidation RT can still provide value even after a full course of chemotherapy (ECOG 1484);
- A combined modality approach is better than maximizing chemotherapy alone in terms of both efficacy and toxicity (SWOG 8736);
- 3 cycles of chemotherapy (and possibly even chemoimmunotherapy) provides inadequate systemic coverage for some early-stage patients (SWOG 8736);

- Older patients without risk factors derive less benefit from consolidation RT (GELA 93-4).

Rituximab/PET-CT Era: Prospective Trials

More recent studies have evaluated treatment programs in which rituximab is incorporated into the treatment regimen and/or PET-CT imaging is used (**Table 1**). These trials are also heterogeneous regarding eligibility criteria and trial design. RT was often not a randomized variable or even included in the treatment programs investigated. Nevertheless, a careful study of these trials can provide helpful guidance on the optimal management of DLBCL in the current era.

The Lymphoma Study Association/Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang trial (LYSA/GOELAMS [NCT00841945]) enrolled 319 patients with nonbulky (<7 cm), stage I/II DLBCL.¹¹ Patients were randomly assigned to 4 to 6 cycles of R-CHOP-14 with or without consolidation RT (40 Gy). Only patients in CR by PET-CT after 4 cycles ($n = 281$) proceeded with treatment according to their random assignment. A negative scan was defined as having “no abnormally increased ¹⁸fluorodeoxyglucose (¹⁸F-FDG) at any site.” The study was designed as a noninferiority study with an original noninferiority margin of 10%, later decreased to 8%.

By intention-to-treat analysis, the LYSA/GOELAMS study demonstrated that R-CHOP was noninferior to R-CHOP plus RT (5-year EFS rate, 89% vs 92%; HR, 0.61; 95% CI, 0.3-1.2; $P = .18$). Crude rates of local failure were 4% (5/137) vs 0% (0/144). Several nuances of this study deserve attention. First, 62 patients (~20%) had a negative staging PET-CT after diagnostic excisional biopsy. This would significantly dilute the effect of

consolidation RT. Further, 8 patients randomized to receive consolidation RT declined treatment. Since nonadherence to an allocated treatment in noninferiority studies will bias results in favor of the investigational arm, a per-protocol analysis is typically standard with such trial designs. Yet, no per-protocol analysis was reported for this trial. Finally, 94% of patients had a very favorable modified IPI score (0-1).

The FLYER study (NCT00278421) did not examine the role of RT in early-stage DLBCL but has influenced RT recommendations.¹² Patients 60 years and younger with nonbulky (<7.5 cm) DLBCL and high-grade B-cell lymphoma (HGBCL), without risk factors such as elevated lactate dehydrogenase (LDH) or poor performance status, were randomly assigned to 4 cycles of R-CHOP with 2 additional cycles of rituximab or to 6 cycles of R-CHOP. PET-CT imaging was not standardized within the protocol. This study had 588 evaluable

patients and used a noninferiority design with a margin of 5.5%. The PFS rate at 3 years did not differ between arms (96% vs 94%) in the intention-to-treat analysis. A per-protocol analysis (n = 482) showed similar findings (98% vs 94%). The investigators concluded that young patients without risk factors can be successfully treated with 4 cycles of R-CHOP with 2 additional cycles of rituximab.

The Intergroup National Clinical Trials Network Study S1001 (NCT01359592), like the FLYER trial, did not specifically investigate the role of consolidation RT in early-stage DLBCL.¹³ In this phase 2 trial, patients with nonbulky (<10 cm) stage I to II DLBCL or HGBCL with or without gene rearrangements and with an ECOG performance status of 0 to 2 were eligible. Patients received 3 cycles of R-CHOP and then underwent an interim PET-CT. Those with a negative PET-CT (Deauville 1-3) received an additional cycle of R-CHOP without consolidation RT. Patients with a positive PET-CT

(Deauville 4-5) received consolidation RT (36-45 Gy) followed by ibritumomab tiuxetan.

In general, patients in the S1001 study had more risk factors than those on the LYSA/GOELAMS or FLYER studies but were still relatively low risk (70% stage-modified IPI 0-1). All gross disease was resected in 10% of patients before initiating systemic therapy. More than half (54%) were older than 60 years, an elevated LDH was noted in 15%, and 3% had a performance status of 2. A negative PET-CT was achieved in 110 of 128 patients (86%) after 3 cycles of R-CHOP. Among patients with a negative interim PET-CT who received 4 cycles of R-CHOP, 5-year PFS and OS rates were 89% and 91%, respectively. Among the 14 patients with a positive interim PET-CT, all but 1 received consolidation RT. With the addition of RT, the 5-year PFS rate was 86%, similar to that among patients who had a negative interim PET-CT. Only 2 of these patients relapsed: 1 refused RT and 1 received just a single cycle of chemotherapy

TABLE 1. Select Randomized Trials in Early-Stage DLBCL

Study	N	Disease characteristics, stage	Randomization	Progression-free survival rate ^a	Comments
Pre-rituximab/PET-CT era					
SWOG ^{4,7}	401	I II (nonbulky)	CHOP × 8 CHOP × 3 + RT	64% 77% (P = .03)	No difference with long follow-up
ECOG ³	172	I (high risk) II	CHOP × 8 CHOP × 8 + RT	56% 73% ^b (P = .05)	Only patients in CR by CT were randomized
GELA 93-4 ⁶	576	I-II without risk factors	CHOP × 4 CHOP × 4 + RT	61% 64% (P = .6)	Only patients 60 years or older
Rituximab/PET-CT era					
LYSA/GOELAMS ⁸	301	I-II nonbulky	R-CHOP × 4-6 R-CHOP × 4-6 + RT	89% 92% (P = .18)	In PET-CT CR
FLYER ⁹	592	I-II nonbulky	R-CHOP × 4 + 2R R-CHOP × 6	96% 94% ^c (P = NS)	No risk factors

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; DLBCL, diffuse large B-cell lymphoma; GELA, Groupe d'Étude des Lymphomas de l'Adulte; LYSA/GOELAMS, Lymphoma Study Association/Groupe Ouest-Est des Leucémies et des Autres Maladies du Sang; NS, not significant; R, rituximab; RT, radiation therapy.

^a5-year, unless otherwise noted; ^b6-year; ^c3-year.

before going off treatment.

The following conclusions can be drawn from modern studies conducted in the rituximab/PET-CT era:

- Chemoimmunotherapy alone, typically with 4 cycles of R-CHOP, provides excellent outcomes in patients with favorable-risk disease who achieve a CR by PET-CT (LYSA/GOELAMS, FLYER);
- Recent studies have excluded patients with bulky disease (variably defined) and almost exclusively enrolled patients with more favorable characteristics compared with the older ECOG and SWOG studies (LYSA/GOELAMS, FLYER, S1001);
- Consolidation RT should be considered for patients who achieve only a PR on interim or postchemotherapy PET-CT (S1001);
- Patients with bulky disease (≥ 7.5 cm) appear to benefit from consolidation RT (see subsequent discussion on RICOVER-60/RICOVER-noRTh and UNFOLDER studies below, which included early-stage disease).

Consolidation RT: Advanced-Stage DLBCL

Patients with stage III to IV DLBCL are at higher risk of recurrence than those with localized disease. A number of different strategies have been explored to improve outcomes, including incorporation of rituximab,¹⁴ more chemotherapy cycles,¹⁵ more intense chemotherapy¹⁶ or chemoimmunotherapy regimens,¹⁷ dose-dense chemotherapy,^{18,19} maintenance rituximab,²⁰ and high-dose chemotherapy and autologous stem cell transplantation (ASCT).²¹ Of these, only the incorporation of rituximab has consistently proved beneficial, and 6 cycles of R-CHOP remains the cornerstone of treatment.

One strategy that has not been studied

in depth is consolidation RT. Most recurrences after R-CHOP, even when a CR is achieved by PET-CT, occur at originally involved sites.²² Several retrospective studies have suggested a benefit for consolidation RT,²²⁻²⁴ but well-designed randomized studies are lacking.

The RICOVER-60 (NCT00052936), and the subsequent RICOVER-noRTh trial amendment, primarily enrolled patients with advanced disease (50% and 60%, respectively).²⁵ The original RICOVER-60 trial was a randomized study that investigated different chemoimmunotherapy regimens in older adults (aged 61-80 years) with both early and advanced DLBCL. Those with bulky (≥ 7.5 cm) or extranodal disease were to receive RT to those areas if a CR or PR was achieved by CT imaging. The original study found that 6 cycles of R-CHOP-14 with 2 additional cycles of rituximab and RT as outlined above achieved the best outcomes. The RICOVER-noRTh trial was an amendment to the original trial in which the optimal chemoimmunotherapy regimen was administered but without RT to bulky or extranodal disease. Comparing outcomes from the 2 studies, the risk of relapse in patients with bulky disease achieving a CR was higher when RT was not administered (22% vs 4%; $P = .007$). A per-protocol analysis of all patients with bulky disease revealed improved PFS in patients receiving RT (88% vs 62%; $P < .001$). Of course, these were not randomized comparisons but they suggest that RT improves outcomes in the setting of bulky disease. A limitation of this study was the lack of PET-CT imaging.

The UNFOLDER trial (NCT00278408) enrolled patients 60 years or younger with high-grade non-Hodgkin lymphomas (NHLs), including DLBCL, presenting with an age-adjusted IPI (aaIPI) of 1 or aaIPI of 0 with bulky disease (≥ 7.5 cm).²⁶ Patients were randomized to

R-CHOP-14 or R-CHOP-21 with a secondary randomization to consolidation RT or observation. PET-CT imaging was not used. A planned interim analysis demonstrated a significantly better 3-year EFS rate for patients randomized to RT (84% vs 68%; $P = .001$), in part because patients randomized to observation who achieved only a PR (by CT imaging) to chemotherapy proceeded to RT and were scored as an event. This study is published in abstract form only.

A recent retrospective study from British Columbia is notable.²⁷ Per institutional policy, patients with advanced DLBCL were initially treated with at least 6 cycles of R-CHOP. Only patients who were PET positive at the completion of chemoimmunotherapy received consolidation RT. Patients who achieved a complete response by PET-CT with R-CHOP experienced a 3-year time-to-progression rate of 83% without consolidation RT. However, survival curves demonstrated a continued risk of progression over time. Notably, patients who were PET positive at the completion of chemoimmunotherapy and received consolidation RT had outcomes similar to the PET-negative cohort and far better outcomes than those who were PET positive but did not receive RT. Neither bulky disease nor skeletal involvement were prognostic in the cohort of patients who achieved a CR by PET-CT. Given the favorable outcomes in the PET-positive cohort after consolidation RT (a population at very high risk of progression) and the relatively high risk of recurrence (~25%) in the PET-negative cohort, it seems logical to hypothesize that consolidation RT may be fruitful even after a CR is achieved.

A retrospective analysis of 9 prospective trials of the German High-Grade Non-Hodgkin Lymphoma Study Group evaluated 292 patients with skeletal involvement, 60% of whom had stage III to IV disease.²⁸ Consolidation RT

PERSPECTIVE BY

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Radiation Therapy in Diffuse Large B-Cell Lymphoma: A Little Boost Gets You Over the Finish Line

Recent advancements in systemic therapies for diffuse large B-cell lymphoma (DLBCL) have revolutionized outcomes and prognosis. Chemotherapy, conjugate antibody systemic therapy, transplant therapy, and chimeric antigen receptor (CAR) T-cell therapy are currently the dominant therapeutic options for DLBCL. Radiation therapy (RT), historically the key treatment for DLBCL, has been swept aside in favor of systemic therapies that are presumed less toxic and more efficacious.

Despite the excellent outcomes with the current upfront PET/CT response-based treatment in early-stage DLBCL without RT,^{1,2} one must not overlook certain situations in which RT can have an important positive impact on outcomes. The predominant pattern of relapse of DLBCL following chemotherapy involves the original sites of disease, even in patients who achieve complete remission (CR).³ Conversely, the predominant pattern of relapse in patients who receive consolidative RT is outside the field of RT.⁴ Such predictable patterns of relapse emphasize the important utility of RT to improve local control in patients with high risk of relapse. This may translate into an event-free survival benefit and eventual overall survival (OS) benefit.

Unfavorable factors associated with increased risk of relapse include bulky disease and skeletal involvement, which have been shown to benefit from consolidative RT.⁵⁻⁹ Further, certain biological factors are associated with increased

risk of relapse, such as activated B-cell, double-hit, and triple-hit histologies.¹⁰ While the additional benefit of RT has not been well studied in these patients, their higher risk of relapse, even among those with early-stage favorable disease,¹⁰ calls for consideration of consolidative RT. Similarly, patients whose PET/CT scan results indicate a slow early response (SER) and/or partial response (PR) to initial systemic therapy are at higher risk of relapse. RT can improve these patients' outcomes to the point where they are comparable with those of patients who achieved CR.^{7,8,10}

The outcomes of DLBCL in the relapsed/refractory (R/R) setting are poor. This calls for treatment escalation to help improve outcomes. RT plays an important role in the peritransplant¹¹ and peri-CAR T-cell settings.¹² As the authors mentioned, RT improves outcomes when offered as part of the peri-autologous stem cell transplant (ASCT) regimen. The benefit may be most evident in patients who have bulky or limited sites of disease, or those with a pre-ASCT PR. Similarly, RT is promising as a bridge to CAR T-cell, with a favorable impact beyond palliating symptomatic sites and improving rates of CAR T-cell infusion. Recent work has shown the predominant pattern of relapse following CAR-T in unirradiated patients to involve preexisting sites of disease.¹³ This highlights the possibility of using RT to augment local control and durable response rates in patients who present with limited disease

prior to CAR T-cell infusion. Patients with limited disease who received comprehensive bridging RT had a trend to better progression-free survival compared with those who did not receive RT.¹³ The 1-year local control rate of disease sites bridged with RT is greater than 80%.¹²⁻¹⁴ This is impressive when compared with the CAR T-cell therapy historical 1-year durable response rate of about 50%.¹⁵⁻¹⁷ We agree with the authors that patients who present with limited disease prior to CAR T-cell therapy should be treated comprehensively to definitive RT doses. There are no clear data or guidelines on the recommended dose of bridging RT. One might consider escalating the dose in the presence of high-risk features that can predict in-field local failure, which include, but are not limited to, bulky tumor size, Myc/BCL rearrangements,¹⁴ and high tumor metabolic volume.¹⁸

The combination of a narrow bridging time window and late referrals to radiation oncology constitutes a major challenge for definitive bridging RT attempts. At our institution, we have addressed this challenge with accelerated treatment using twice-daily radiation treatment and early referrals to radiation oncology whenever possible. For patients who present with diffuse disease prior to CAR T-cell therapy, palliative low-dose RT may be sufficient to control both symptoms and disease. R/R DLBCL is radiosensitive, and low-dose RT is sufficient to reprime the immune system and sensitize

the lymphoma cells to CAR T-cell therapy.^{19,20}

Despite all the first- and second-line treatment efforts, a significant number of DLBCL patients relapse. At that point, multiple other systemic treatment options can be offered, and RT can provide palliative treatment. However, a subset of patients might still benefit from curative RT. For instance, patients with 1 site of relapse following ASCT had improved OS when treated with salvage RT compared with salvage chemotherapy.²¹ This might also apply to patients with limited relapsed disease, post CAR T-cell therapy; recent data show a survival benefit with comprehensive salvage RT.²²

RT toxicity was a major concern when it was delivered as a systemic therapy—eg, total body irradiation, total lymphatic irradiation, or subtotal lymphatic irradiation. Doses prescribed to these large fields were sometimes up to 40 to 50 Gy. However, modern RT utilizes lower doses.²³ It is more targeted and utilizes contemporary fields²⁴ and techniques, which leads to reduced doses to the organs at risk, minimizing the acute and late-RT toxicity. The International Lymphoma Radiation Oncology Group has developed expert consensus for treating extranodal and nodal NHL using involved-site radiotherapy (ISRT). These fields are much smaller and more personalized to the patient's initial sites of involvement compared with the previously used involved-field radiotherapy. Toxicity can be further lowered by using newer techniques available, including intensity-modulated radiotherapy and proton therapy for disease located in critical locations such as the mediastinum.^{25,26} While data on late effects with contemporary techniques are immature, early data have demonstrated that they are safe and effective.²⁷⁻²⁹

In summary, selected patients

with DLBCL have excellent outcomes without RT. However, ISRT in the upfront or R/R setting may prolong remission and avoid subsequent toxic therapeutic approaches when offered to the right subset of patients, who include those with unfavorable characteristics and/or predictable site of relapse (ie, limited disease, bulky disease, SER/PR). ■

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For full reference list, visit cancernetwork.com/Hoppe_12.22

to osseous sites was associated with improved EFS. As in RICOVER-noRTh, PET-CT imaging was not used. Finally, the RICOVER-noRTh study demonstrated a benefit for RT in bulky disease, and it consisted largely of patients with advanced disease (60% of all patients and 77% of those with bulky disease).²⁵

Consolidation RT: Treatment Recommendations

Given the data heretofore discussed, we recommend the following for patients who have achieved a CR with chemoimmunotherapy. For patients with stage I to II nonbulky DLBCL with 0 to 1 IPI risk factors, 4 cycles of R-CHOP or 3 cycles of R-CHOP plus RT (30 Gy) are reasonable options. For stage I to II nonbulky DLBCL with ≥ 2 IPI risk factors, consolidation RT (30 Gy) can be considered after completing chemoimmunotherapy depending upon distribution of disease, response to therapy, risks of RT, etc. We recommend consolidation RT in patients with early or advanced disease in the presence of bulky disease (variably defined in randomized studies; most commonly, >7.5 cm). Select patients with advanced DLBCL without bulky disease can also be considered for consolidation RT, including those with limited skeletal involvement (1-2 sites) or disease located in sensitive areas. A prospective study by the International Lymphoma Radiation Oncology Group is assessing whether 20 Gy is sufficient in the setting of a complete response by PET-CT (Deauville 1-3). In the setting of a partial metabolic response (Deauville 4), a higher dose of RT would be appropriate (40-44 Gy).

Relapsed/Refractory DLBCL CAR T-Cell Therapy

The majority of patients diagnosed with DLBCL will achieve long-term remission with chemoimmunotherapy. Nevertheless, 20% to 50% of patients will have either primary refractory disease or

TABLE 2. Select Retrospective Studies Comparing Outcomes of Patients Treated With Peritransplant RT

Institution/group	Timing	Fields	Dose	Result
PARMA Study Group ⁴³	Pre-ASCT	Bulky disease >5 cm; extranodal disease	1.3 Gy BID; 26 Gy total	RT: 8/22 (36%) relapsed No RT: 18/33 (54%) relapsed
University of Chicago ⁵²	Pre-ASCT: n = 1 Post ASCT: n = 6	Bulky or persistent disease	24-58 Gy	RT: 0/7 (0%) failed at prior sites No RT: 16/39 (41%) failed at prior sites
University of Utah ⁵³	Pre-ASCT: n = 19 Post ASCT: n = 31 Both: n = 3	Variable	NS	RT associated with inferior DFS and no difference in OS; many patients in “no RT” group received TBI
Memorial Sloan-Kettering ⁵⁴	Pre-ASCT	Limited disease, bulky disease (≥5 cm), residual masses	1.5 Gy BID to 30 Gy (18 Gy if TBI utilized)	RT: 94% local control No RT: 60% RT associated with improved PFS on MVA
University of Rochester ⁵⁵	Post ASCT	Variable	CR: 20-26 Gy PR: 30 Gy Refractory: 30-36 Gy	RT: 37/78 (47%) relapsed No RT: 47/83 (57%) relapsed RT associated with improved DFS and OS on MVA
Autologous Blood and Marrow Transplant Registry ⁵⁶	Post ASCT	Variable	NS	RT was associated with improved survival on MVA

ASCT, autologous stem cell transplant; BID, twice daily; CR, complete response; DFS, disease-free survival; MVA, multivariable analysis; NS, not stated; OS, overall survival; PFS, progression-free survival; PR, partial response; RT, radiation therapy; TBI, total body irradiation.

will experience relapse after achieving a CR to systemic therapy. Second-line chemotherapy, typically followed by high-dose chemotherapy and ASCT, has until recently been the most common approach for these patients. Unfortunately, approximately half of patients with R/R DLBCL are not transplant candidates due to age and/or comorbidities; more than 60% of patients with R/R DLBCL will fail to respond to second-line chemotherapy; and about 50% of patients undergoing ASCT will relapse again despite this procedure.²⁹

In 2017, the US FDA approved a novel therapy for R/R DLBCL: CAR T-cell therapy. CAR T cells are a type of adoptive cellular transfer immunotherapy, consisting of autologous T cells that are harvested from a patient and then genetically engineered to express chimeric antigen receptor molecules that can target a specific antigen of interest on malignant cells. CD19, a transmembrane protein expressed on all B cells, has proved to be an ideal

target for DLBCL. In a typical course, patients undergo leukapheresis, wait a minimum of 2 weeks for the CAR T-cell production process, and are then treated with lymphodepleting chemotherapy several days prior to infusion of the autologous CAR T-cell product. This allows for optimal CAR T-cell survival, expansion, and tumor cell killing upon reinfusion. The genetic engineering breakthrough of CAR T cells, which combine the exquisitely specific antigen-recognition capabilities of antibodies with the downstream cytotoxic effector functions of T cells, has generated considerable interest as one of the most enterprising and technically advanced forms of immunotherapy available.

Three seminal phase 2 clinical trials—JULIET (NCT02445248), ZUMA-1 (NCT02348216), and TRANSCEND-NHL-001 (NCT02631044)—demonstrated overall response rates (ORRs) between 52% and 82% and CR rates between 40% and 54%,

with sustained PFS rates around 40% following a single infusion of the engineered cellular product.³⁰⁻³² Four autologous CD19-directed CAR T-cell therapies are currently FDA approved for R/R DLBCL: axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), brexucabtagene autoleucel (brexu-cel), and lisocabtagene maraleucel (liso-cel).

While CAR T-cell therapy continues to evolve, several major challenges persist affecting utilization (eg, cost), tolerance (eg, cytokine release syndrome [CRS] and immune effector cell-associated neurotoxicity syndrome [ICANS]), inherent treatment delays, and efficacy. For example, it may take up to 2 months to obtain insurance approval and then manufacture the CAR T-cell product, which necessitates some form of bridging therapy in many patients (discussed in more detail below). Further, about 60% of patients relapse despite CAR T-cell therapy. A European cohort study of 116 patients treated with axi-cel and

tisa-cel for R/R DLBCL revealed that high baseline total metabolic tumor volume (the volume of tumor on PET-CT) at the time of infusion, increased C-reactive protein, and multiple involved extranodal sites were all predictive of early disease relapse.³³ High tumor burden was also associated with a higher risk of recurrence and greater toxicity in ZUMA-1 and in a series from Moffitt Cancer Center.^{34,35}

CAR T-Cell Therapy and Bridging Therapy

CAR T-cell production is a multistep process that requires several weeks between T-cell harvesting and reinfusion. In some clinical trials, bridging therapy was allowed during this time frame for patients with symptomatic disease. The intention of bridging therapy is both to provide immediate palliation of symptoms and to prevent disease progression that may jeopardize success of the upcoming CAR T-cell intervention. Bridging therapy may consist of steroids, chemotherapy, immunotherapy, targeted agents, and/or RT.³⁶ Hematologic malignancies, including DLBCL, are inherently sensitive to RT. As many patients with R/R DLBCL are refractory to chemoimmunotherapy, RT may be an ideal bridging modality.

There are currently few published studies evaluating bridging RT in DLBCL. One of the first case series was from the Moffitt Cancer Center.³⁷ Patients with high-risk DLBCL ($n = 6$) or HGBCL with *MYC* and *BCL2* and/or *BCL6* rearrangements ($n = 6$) who were treated with bridging RT prior to axi-cel were evaluated. Bulky disease was present in 6 of the 12 patients. Median dose of RT was 20 Gy (range, 6-30 Gy). Patients tolerated RT well, with improvement in symptoms in most patients, no unanticipated adverse effects after CAR T-cell administration, and early outcomes consistent with published studies.

A study from The University of

Texas MD Anderson Cancer Center (MDACC) illustrates the difficulty in evaluating outcomes after bridging therapy.³⁸ Two cohorts of patients with R/R DLBCL were compared: 81 patients received bridging therapy prior to planned axi-cel, and 67 patients did not. Bridging therapy consisted of either systemic therapy alone, RT alone, or RT combined with systemic therapy. As expected, patients requiring bridging therapy had higher-risk disease and inferior PFS rates (20% vs 40% at 1 year; $P = .01$) and OS rates (48% vs 65% at 1 year; $P = .05$), in part because many patients who received bridging therapy never ultimately received axi-cel. Among the 3 bridging strategies, those patients who received RT alone had an improved median PFS of 8.9 months, compared with a median PFS of 4.7 months for the cohort that received systemic therapy alone ($P = .05$). Additionally, bridging RT was associated with increased CR compared with systemic therapy (82% vs 38%; $P = .01$). Comprehensive RT (treating all sites of active disease), compared with focal RT (treating only select sites), seemed to be associated with improved outcomes (1-year PFS rate, 57% vs 17%; $P = .12$). Given that the proportions of patients with IPI of at least 3 ($P = .48$), bulky disease ($P = .73$), and elevated LDH ($P = .09$) at the time of leukapheresis were not significantly different between RT and systemic therapy groups, this result suggests that RT may be an effective bridging modality in patients with R/R DLBCL. Larger studies are needed to evaluate this further.

Arscott et al evaluated 41 patients enrolled on a phase 2a study of tisa-cel for various hematologic malignancies, including DLBCL.³⁹ Patients were divided into 2 groups: those who received RT prior to CAR T-cell infusion and those who had never received RT. The RT cohort was further divided into 3 subgroups: induction RT (<30 days prior

to infusion), prior RT (>30 days but <12 months prior to infusion), and remote RT (>12 months prior to infusion). One-year PFS and OS rates in the “no RT” vs “induction RT” groups were 44% vs 78% and 65% vs 100%, respectively. Moreover, grade 3 or higher CRS occurred in 10 of 41 patients overall but in no patients within the induction RT group. The use of radiation therapy did not affect CAR T cell expansion or timing of peak CAR T cell counts.

Finally, a series from the University of Pennsylvania evaluated 31 patients receiving either tisa-cel or axi-cel for R/R DLBCL, 5 of whom received bridging RT.⁴⁰ None of the patients receiving bridging RT developed grade 3 or greater CRS or ICANS, whereas the risks of grade 3 or greater CRS and ICANS were 23% and 15%, respectively, among patients who did not receive bridging RT. Clinical outcomes were similar among the 2 groups. Findings from these studies suggest that RT does not impact the efficacy of anti-CD19 CAR T-cell therapy, may improve outcomes in select patients, and may reduce the risk of CRS and ICANS.

Three cohorts of patients may be ideal candidates for bridging RT prior to CAR T-cell therapy. First, RT should be considered for patients with symptomatic disease that is refractory to systemic therapy. Maintaining performance status and controlling pain and other symptoms will help the patient better tolerate the CAR T-cell procedure. Second, patients with bulky disease, or with disease that threatens such organs as the spinal cord or airway at the time of leukapheresis, may also benefit from bridging RT. Bulky disease is known to decrease the efficacy of CAR T-cell therapy, presumably by overwhelming the ability of the immune system to eradicate the entire extent of disease.^{34,41} Third, it may be appropriate to consider bridging RT in patients with localized

refractory disease. Treating all gross disease with RT, followed by CAR T-cell therapy, may optimally leverage both modalities and increase the likelihood of success.

The optimal RT schedule, timing, and other such issues remain to be clarified; they are likely dependent on a number of patient-specific factors, including the anatomical location and extent of disease. Nevertheless, certain suggestions and inferences can be drawn from the available data while major consensus awaits the results of clinical trials.

Regarding timing, it seems advisable to delay RT until after apheresis has taken place. Even with low RT doses and minimal bone marrow exposure, circulating lymphocytes within the bloodstream remain susceptible to RT. Prior studies primarily treated patients after apheresis (84% for Moffit, 65% for MDACC, 100% for University of Pennsylvania).^{37,38,40} Such concerns must be counterbalanced against the need to treat patients with symptomatic disease awaiting insurance approval, etc.

The optimal dose for bridging RT is also uncertain. In some circumstances, the dose is limited by logistical timing of the CAR T-cell schedule. While many patients have been treated with palliative doses (20-30 Gy), at least 1 study suggests that “definitive” doses may be ideal. Sim et al demonstrated that local control was 100% in patients who received at least an equivalent total dose in 2 Gy fractions (EQD2) of 39 Gy.³⁴ Of the 12 patients (40%) in this series who progressed despite receiving bridging RT, 8 (67%) experienced progression within the prior RT fields as part of their relapse, while only 4 (33%) progressed systemically, illustrating the importance of local control. Moreover, 7 of the 9 in-field lesion failures that were seen in this series had a baseline lesion of metabolic tumor volume (MTV) greater than 50 cm³. Very low doses of bridging RT (2-4 Gy × 2) are being considered

with the goal of immune “priming.” However, there have not been any clinical reports using this strategy to date. The utility of higher doses and prolonged fractionation schemes must be weighed against the putative benefits of shorter RT courses allowing more prompt CAR T-cell infusion.⁴²

Bridging RT: Treatment Recommendations

For patients with localized presentations that can be safely encompassed in RT fields, we recommend comprehensive treatment, ideally to definitive doses (eg, ~40 Gy). This can often be accomplished in a hypofractionated manner (eg, 3 Gy per fraction) to expedite treatment and minimize reinfusion delays. If definitive doses are not feasible or practical given the circumstances, a total dose of 20 Gy to 30 Gy in 2 Gy to 4 Gy fractions could be pursued.

Patients with more extensive disease who present with bulky tumors, symptomatic disease, or lymphoma in sensitive locations (eg, spinal cord, airway), we suggest localized irradiation of select sites to a dose of 20 Gy to 30 Gy. Hypofractionation is often feasible (see below).

ASCT and RT

In the PARMA trial, 215 patients with relapsed high-grade NHL were initially treated with second-line chemotherapy.⁴³ Those who had chemotherapy-sensitive disease (n = 109) were randomized to additional conventional chemotherapy or high-dose chemotherapy and ASCT. Consolidation RT (1.3 Gy twice daily to 26 Gy) was given in the ASCT arm for those with extranodal disease and sites of disease bulk at relapse (≥5 cm). The chemotherapy-alone arm also used RT to a slightly higher dose (1.75 Gy daily; 35 Gy total) but limited RT to sites of disease bulk (≥5 cm).

ASCT was associated with statistically significant improvements in rates at 5 years for both EFS (46% vs 12%)

and OS (53% vs 32%), and PARMA established ASCT as a standard for younger patients with R/R DLBCL with chemotherapy-sensitive disease. An analysis of the patterns of failure within the PARMA trial showed that those patients who received RT had fewer relapses (36% vs 55%) compared with patients who did not receive RT, even though the overall irradiated group consisted exclusively of patients with bulky or extranodal disease.⁴⁴ Of the 34 irradiated patients who relapsed, 7 experienced recurrences at initial sites of disease. This contrasts with 38 local failures among 75 patients who did not receive RT. Combined with results of multiple smaller institutional series, these results suggest that RT can play an important role in the setting of ASCT (**Table 2**).

The International Lymphoma Radiation Oncology Group has published detailed guidelines regarding RT in the setting of ASCT.⁴⁴ We generally recommend post-ASCT RT for patients with bulky and/or localized disease at the time of relapse. A dose of 30 Gy is recommended in the setting of a CR, with higher doses reserved for PRs. With the recent FDA approval of axi-cel as second-line therapy for patients with refractory or early-relapsed DLBCL (discussed below), the role of ASCT in R/R DLBCL will likely diminish and will mostly be limited to those with late relapses (>1 year) after primary therapy.

CAR T-Cell vs ASCT

Three trials have compared CAR T-cell therapy with ASCT in R/R DLBCL. The ZUMA-7 trial (NCT03391466) compared axi-cel with ASCT for patients with refractory or early-relapsed (<12 months) disease and found statistically significant improvements in CR rates (65% vs 32%; *P* <.001) and EFS (8.3 vs 2 months; *P* <.001) in those treated with axi-cel.³¹ Similarly, the TRANSFORM trial compared liso-cel with ASCT for the same population and also observed higher CR rates (66% vs

39%; $P < .001$) and median EFS (10.1 vs 2.3 months; $P < .001$) with the use of CAR T-cell therapy.⁴⁵ Finally, the BELINDA trial (NCT03570892) randomized 300 patients with R/R aggressive lymphoma to tisa-cel or salvage chemotherapy and ASCT, with no significant differences seen in the EFS rate at 3 months, ORR (46% vs 43%), or CR rate (28% each) between arms.⁴⁶ While these 3 trials differ from one another in certain key respects (eg, crossover allowances, stratification factors, cell manufacturing time, and bridging therapy options), the FDA has approved axi-cel therapy as an acceptable second-line therapy for refractory DLBCL or in patients relapsing within 12 months of completing first-line therapy.

RT as a Palliative Modality

RT has an important role in the management of patients with R/R DLBCL with symptomatic disease. Short courses of RT can alleviate a number of different symptoms, including pain, bleeding, airway or bowel obstruction, and neurologic compromise.⁴⁴ Disease that is asymptomatic but threatening critical organs, such as the spinal cord or airway, can also be addressed with RT to prevent impending complications. Finally, RT can also be used as an effective treatment modality for localized progression to delay the need for systemic therapy, which may be associated with a greater adverse effect profile.⁴⁷

In one of the largest and most comprehensive studies of this topic, Tseng et al evaluated 110 patients with R/R DLBCL at Brigham and Women's Hospital/Dana-Farber Cancer Institute who received salvage RT to 121 sites. The median dose was 37.8 Gy (range, 16.5-55.7 Gy).⁴⁸ Despite the poor prognosis of such patients, 84% achieved a response (clinical or imaging) and 80% who presented with symptoms experienced improvement during or immediately after RT. Outcomes were

not improved with higher doses. A study from the University of British Columbia also found that higher doses were not associated with improved outcomes in the palliative setting.⁴⁹ A more recent series from the University of Pennsylvania evaluated outcomes in 92 patients with hypofractionated RT (median dose, 20 Gy) for R/R DLBCL. The ORR was 72% with a CR rate of 53%. Local control at 1 year was 54%.⁵⁰

The optimal doses for palliation of R/R DLBCL remain undefined, and the most suitable regimen may ultimately depend on the clinical scenario. Doses of 20 to 30 Gy administered in a hypofractionated manner are used most frequently. Some studies support the use of very low-dose RT (2 Gy \times 2), which is more commonly used in low-grade NHLs. A phase 2 single-institution study of 25 patients with R/R DLBCL reported an ORR of 70%; 13% to 60% functional improvement on day 21 post treatment; a median response duration of 6 months; and a 1-year local control of 34%.⁵¹ Patients with bulky disease or activated B-cell (ABC) subtype may not respond well to this regimen. Given the small number of patients studied and the short response duration, very low-dose RT for DLBCL may be suitable only for patients with an anticipated life expectancy of less than 6 months.

Palliative RT: Treatment Recommendations

A number of different approaches may be appropriate depending upon the clinical circumstances. For patients with a limited life expectancy, very brief regimens would be preferred, such as 4 Gy \times 5, 8 Gy \times 1, or even 2 Gy \times 2 or 4 Gy \times 1. For patients with a more favorable outlook, especially with a limited burden of disease, more protracted regimens may be more appropriate (eg, 3 Gy \times 10 or 2.5 Gy \times 15). The treatment volumes should normally be restricted to gross disease with a small margin. ■

DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

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