



Critical Review

Role of Radiation Therapy in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma: Guidelines from the International Lymphoma Radiation Oncology Group



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Approximately 30% to 40% of patients with diffuse large B-cell lymphoma (DLBCL) will have either primary refractory disease or relapse after chemotherapy. In transplant-eligible patients, those with disease sensitive to salvage chemotherapy will significantly benefit from high-dose therapy with autologous stem cell transplantation. The rationale for considering radiation therapy (RT) for selected patients with relapsed/refractory DLBCL as a part of the salvage program is based on data regarding the patterns of relapse and retrospective series showing improved local control and clinical outcomes for patients who received peritransplant RT. In transplant-ineligible patients, RT can provide effective palliation and, in selected cases, be administered with curative intent if the relapsed/refractory disease is localized. We have reviewed the indications for RT in the setting of relapsed/refractory DLBCL and provided recommendations regarding the optimal timing of RT, dose fractionation scheme, and treatment volume in the context of specific case scenarios. © 2017 Elsevier Inc. All rights reserved.

Introduction

In patients with diffuse large B-cell lymphoma (DLBCL) treated with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) chemotherapy, approximately 10% to 15% will have primary refractory disease and another 20% to 25% will develop a relapse after an initial response (1). In the PARMA trial, which randomized patients with relapsed/refractory non-Hodgkin lymphoma (NHL) with chemosensitive disease to high-dose therapy with autologous bone marrow transplantation (HDT-ABMT) versus conventional chemotherapy (2), patients in the HDT-ABMT arm had significantly greater 5-year event-free survival (46% vs 12%) and overall survival (OS) (53% vs 32%). However, it has been estimated that only one half of patients with relapsed/refractory NHL will be eligible for transplant, and among these patients, only one half will have chemosensitive disease and thus be able to proceed to transplantation. Even in the rituximab era, according to results from the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study (3), the 3-year progression-free survival (PFS) and OS for patients with refractory/relapsed DLBCL were only 37% and 49%, respectively. CORAL was a randomized trial comparing 2 salvage regimens, rituximab, ifosfamide, etoposide, and carboplatin (R-ICE) versus rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP). As such, in considering the management approaches for patients with relapsed/refractory DLBCL, it is critical to note that therapeutic options are often limited and that only a few patients will achieve long-term cure.

Limited, nonrandomized data are available regarding the role of radiation therapy (RT) in the setting of relapsed or refractory aggressive NHL (2, 4-10). In the present review, we have summarized the available evidence and provided recommendations on the use of RT for relapsed/refractory DLBCL, the most common subtype of aggressive NHL. We

also reviewed the timing of the RT and the dose and volume considerations in the era of modern imaging and RT techniques and new systemic therapies.

For the purposes of our review, we have defined relapsed disease as new lymphoma found on imaging and confirmed by a biopsy after an initial complete response to chemotherapy. We defined refractory disease as biopsy-proven residual disease after primary or salvage chemotherapy according to an increase in ¹⁸F-fluorodeoxyglucose (FDG) avidity or disease volume compared with previous scans that was also confirmed by biopsy. Pathologic confirmation of relapsed or refractory disease is mandatory, with rare exceptions.

Rationale for Considering RT as a Component of Curative Intent Therapy for Patients With Relapsed or Refractory NHL

In an early report evaluating the use of HDT-ABMT among patients with relapsed/refractory aggressive NHL, analysis of sites of further relapses after transplantation showed that 76% of cases of progression were isolated and involved primarily the original site of relapse or refractory disease, indicating that local control is critical (11). Consequently, the PARMA trial used consolidative RT to sites of bulky disease >5 cm as part of the treatment regimen (2). Ultimately, 40% of patients received RT. Fewer relapses occurred among the irradiated patients (36% vs 55%), despite the presence of bulky disease in the RT group.

During the past 2 decades, additional reports of patients with relapsed and refractory disease have further shown that relapses after salvage HDT with autologous stem cell transplantation (ASCT) often involve the initial relapsed or refractory disease sites, despite a complete response to salvage chemotherapy. In the CORAL trial (3), RT was not included as a part of the treatment. Progression or relapse, reported in 104 patients in the R-ICE arm and 97 patients in the R-DHAP arm, was mostly at

the initial sites and developed in one half of the patients during the treatment period. However, the precise number and relapse patterns of those who did or did not proceed to ACST were not provided. In a recent updated report from the University of Rochester (12), 100 patients with relapsed NHL who had achieved remission before HDT-ASCT were analyzed. The patterns of relapse analysis showed that 40% and 76% of early-stage and advanced-stage patients, respectively, had developed relapse at the sites of initial disease. The lower proportion of patients with relapse at the initial sites among early-stage patients might have reflected a more frequent use of RT as a part of the initial treatment in these patients. These data show that local recurrence, despite an excellent response to systemic therapy, is a significant problem and, hence, support the incorporation of consolidative RT as a part of salvage treatment.

For patients without a response to salvage chemotherapy, proceeding with transplantation in the context of chemotherapy-refractory disease has been associated with a poor outcome (11). In the previously described PARMA trial (2), only patients with chemotherapy-sensitive disease were included in the study for randomization to transplant versus conventional chemotherapy. Multiple studies from the positron emission tomography (PET) era have also shown that patients with a complete PET response will fare significantly better than those with residual FDG avidity before undergoing transplantation (13-18). In patients with localized residual FDG-avid disease after chemotherapy, local RT can potentially help achieve a complete metabolic response (6).

The studies of patients with relapsed/refractory NHL undergoing HDT-ASCT and the reported outcomes of patients who did or did not undergo peritransplant RT are summarized in Table 1 (2, 4-10). These studies varied in the timing of RT (before transplantation vs after), radiation volume, and dose. Most showed that the receipt of RT was associated with improved outcomes. However, the findings should be interpreted with caution given the predominantly retrospective nature of the studies, heterogeneity in radiation volumes and doses, and potential selection biases.

General Indications for, and Timing of, RT in the Recurrent/Refractory Setting

Patients with localized relapsed/refractory disease that can be encompassed by an RT field ie, associated with an acceptable toxicity profile should be considered for RT as a part of the salvage regimen. In patients with more disseminated relapse, RT to selected sites can also serve an important role. For example, sites that were bulky at relapse might benefit from RT. In previous studies, 5 cm was used as a cutoff for bulky disease in the relapsed/refractory setting (2, 19). Locoregionally confined sites with an incomplete response to salvage chemotherapy should also be considered for RT. Extrapolating data from the subgroup analysis of the MInT and RICOVER-60 trials of patients with DLBCL with skeletal involvement, patients with dominant skeletal relapses might also benefit from RT. In

that analysis (20), the addition of RT was associated with a 70% improvement in event-free survival ($P < .001$). Additionally, RT should be strongly considered for sites in which local control is especially critical, including relapsed disease causing or threatening spinal cord compression, nerve root compression, and obstruction of the superior vena cava, upper aerodigestive tract, or urologic tract.

The timing of the peritransplant RT in reported series has varied (Table 1). A key advantage of pretransplant RT is that it can potentially cytereduce localized residual active disease before HDT-ASCT. A study from the Memorial Sloan Kettering Cancer Center (MSKCC) on relapsed/refractory DLBCL with chemosensitive disease, defined as a $\geq 50\%$ reduction in the computed tomography (CT) volume after second-line chemotherapy, compared the outcomes of patients treated with or without pretransplant RT (6). Of the 17 patients with persistent FDG-avid disease after salvage chemotherapy before HDT-ASCT, 3 of the 5 who did not receive pretransplant RT developed a relapse, all at the previous FDG-avid sites. In contrast, only 4 of the 15 who had received pretransplant RT developed a relapse. The disadvantages of pretransplant RT include an increased risk of toxicity during transplantation such as pneumonitis (see special consideration to limit lung doses under "Scenario 7: Relapsed/Refractory Primary Mediastinal Large B-Cell Lymphoma"), veno-occlusive disease, and more exaggerated dermatitis, mucositis, or enteritis, depending on the RT sites (21-23). In a study comparing 14 patients who underwent pretransplant abdominopelvic involved-field (IF) RT and 19 who underwent post-transplant IFRT, pretransplant IFRT was associated with a trend toward increased grade 3/4 gastrointestinal toxicity (31% vs 6%; $P = .094$) (24). A comparison of relapse rates between the pre- and post-transplant RT was not provided. Delay in transplantation to deliver pretransplant RT is another potential concern but can be mitigated by an accelerated RT program, delivering the RT twice daily. Post-transplant RT has a lower toxicity profile, although this option is limited to patients with an adequate response to salvage chemotherapy before transplantation. Additionally, post-transplant RT allows for a more tailored decision on the final RT dose that depends on the overall response to systemic therapy. It can also allow for a smaller RT volume when the post-transplant tumor volume has decreased, and toxicity concerns about more generous volumes exist. However, post-transplant RT has the theoretical disadvantage of exposing reinfused stem cells to RT, especially when the treatment volume includes a large amount of bone marrow, potentially leading to prolonged cytopenia. In addition, the logistical concern exists of missing the window for post-transplant RT delivery if the patient's recovery from transplantation is prolonged.

Case Scenarios

We have provided our RT recommendations for different case scenarios of relapsed/refractory DLBCL (summarized

Table 1 Studies comparing outcomes of patients with relapsed or refractory NHL treated with or without peritransplant RT

Investigator	Patients (n)	RT timing	RT field	RT dose	Results (RT vs no RT)
Philip et al (2), 1995	22 RT/33 no RT	Before Tx	Bulk >5 cm	26 Gy (1.5 BID)	RT, 8/22 (36%) relapsed; no RT, 18/33 (54%) relapsed
Mundt et al (10), 1997	10 RT/46 no RT	Both before and after Tx	IFRT (encompassing only known disease sites with 2-cm margins)	Mean dose, 40 Gy (range 24-58)	RT: 4-y LC, 100%; no RT: 4-y LC, 61%
Vose et al (4), 2001	46 RT/105 no RT	After Tx	IFRT	Post-Tx RT dose NR	MVA: RR of death without RT, 1.6 (P = .05)
Friedberg et al (5), 2001	152 RT/400 no RT (including indolent NHL)	Before Tx	Mediastinum, 26%; abdomen/spleen, 25%; pelvis, 16%; other, 33%	Pre-Tx RT dose NR	RT: median OS, 94 mo; no RT: median OS, 121 mo (P = .02); 25% vs 5% died of respiratory causes with vs without axillary/mediastinal RT
Wendland et al (9), 2007	53 RT/114 no RT	Both before and after Tx	IFRT	Median dose, 28.8 Gy (range 21-43.2)	RT (significantly more likely to have bulky or extranodal disease): 5-y OS, 40%; LC, 69%; no RT: 5-y OS, 47%; LC, 72%
Hoppe et al (6) 2009	47 RT/36 no RT (all had PET/CT before Tx)	Before Tx	IFRT, limited to ≤2 involved LN regions	30 Gy (1.5 BID); 18 Gy (1.5 BID) if with TBI	RT: crude LC, 94%; no RT: crude LC, 60% (P = .006); RT improved PFS (P = .02); PET, 3/34 vs 11/31 relapsed; no RT, 79% of relapses were at previous sites
Biswas et al (7), 2009	79 RT/85 no RT	After Tx	Encompassed known sites of disease recurrence	CR, 20-26 Gy; PR, 30 Gy; persistent disease, 30-36 Gy	MVA: RT improved DSS (HR 0.39; P = .01) and OS (HR 0.35; P = .002); no RT, 55% of relapses were at previous sites
Coutu et al (8), 2015	13 RT/59 no RT	After Tx	Persistent nodal masses after Tx ≥ 2 cm	30.6 Gy	With residual nodal mass >2 cm (n = 19), RT improved LC, DFS, and OS

Abbreviations: BID = twice daily; CR = complete response; DFS = disease-free survival; DSS = disease-specific survival; HR = hazard ratio; IFRT = involved-field radiation therapy; LC = local control; LN = lymph node; MVA = multivariate analysis; NHL = non-Hodgkin lymphoma; NR = not reported; OS = overall survival; PET/CT = positron emission tomography/computed tomography; PFS = progression-free survival; PR = partial response; RR = relative risk; RT = radiation therapy; TBI = total body irradiation; Tx = transplantation.

in Table 2). The first 2 case scenarios are of patients with relapsed/refractory disease sensitive to salvage chemotherapy and being considered for peritransplant RT. The third case scenario regards the role of RT for patients who are potential transplantation candidates but have localized sites that are refractory to primary or salvage chemotherapy. In the fourth case scenario, we describe our recommendations for RT use for patients who are not transplant candidates. The remaining 3 case scenarios address the role of RT in special situations.

Scenario 1: Relapsed or refractory disease after primary chemotherapy with a complete metabolic response (Deauville 1-3) to salvage chemotherapy

A case example of scenario 1 is shown in Fig 1. Evidence supporting the use of peritransplant RT in

the setting of a complete metabolic response to salvage chemotherapy (Deauville 1-3) is limited, because most of the studies were from the pre-PET era. The study from the MSKCC on pretransplant RT for relapsed/refractory DLBCL with chemosensitive disease to second-line therapy (defined as ≥50% reduction in the largest nodal masses on CT) has provided data on the relevance of pre-HDT/ASCT PET findings (6). Among the 65 patients with negative PET findings after salvage chemotherapy and before HDT-ASCT, 11 of 31 patients (35.5%) who had not undergone RT developed a relapse compared with only 4 of 34 patients (11.8%) who had received RT (6). A lower relapse rate was observed in those who had received RT, although the irradiated patients had initial sites of ≥5 cm or residual nodal masses of ≥2 cm. All relapses were outside the irradiated field. The high relapse rate in the patients who had not received RT,

Table 2 Radiation therapy recommendations for specific case scenarios of relapsed/refractory lymphoma

Scenario 1: Relapsed or refractory disease after primary chemotherapy, with complete metabolic response (Deauville 1-3) to salvage chemotherapy
Timing
Post-transplant RT: within 4-12 wk after transplantation depending on recovery (preferred)
If pretransplant RT per institutional preference: within 4 wk (but as soon as practical) after most recent salvage chemotherapy course
Dose
Post-transplant RT: 30-36 Gy in 1.5-2 Gy/fraction
Pretransplant RT: 30-36 Gy in 1.5-2 Gy/fraction or 30 Gy in 1.5 Gy/fraction BID per MSKCC regimen
Volume
Nodal relapsed/refractory disease: limit to nodal sites of relapse, but consider concluding adjacent nodal disease that responded to first-line chemotherapy if its inclusion is not associated with significant toxicity
Extranodal relapsed/refractory disease: follow ILROG ISRT principles
Scenario 2: Relapsed or refractory disease after primary chemotherapy with overall reduction in FDG uptake, but focus/foci of residual FDG avidity (Deauville 4-5) after salvage chemotherapy
Timing
Pretransplant RT (favored): within 4 wk (but as soon as practical) after most recent course of salvage chemotherapy; perform stem cell harvest before initiation RT especially if a large bone marrow volume is included in the RT field
Post-transplant RT (if not referred prior to transplant): within 4-12 wk post-transplant depending on recovery
Dose
Pretransplant: 36 Gy in 1.8- 2 Gy/fraction, with either a sequential or integrated boost to a final dose of 40-45 Gy in 1.8-2.2 Gy/fraction to the site of residual FDG-avid focus
Post-transplant:
if restaging PET/CT scan shows complete metabolic response (Deauville 1-3): 36 Gy in 1.8-2 Gy/fraction;
if restaging PET/CT scan shows residual FDG avidity (Deauville 4-5): 36 Gy in 1.8-2 Gy/fraction with either sequential or integrated boost to final dose of 40-45 Gy in 1.8-2.2 Gy/fraction
Volume
Same as that for Scenario 1
Scenario 3: Localized refractory disease to primary or salvage chemotherapy
Timing
Pretransplant RT: within 4 wk (but as soon as practical) after most recent salvage chemotherapy course; perform stem cell harvest before initiation RT, especially if large bone marrow volume is included in RT field
Dose
40-50 Gy in 1.8-2 Gy/fraction OR consider 35-40 Gy in 1.3-1.5 Gy/fraction BID if evidence of rapidly progressive disease
Volume
Same as that for Scenario 1
Scenario 4: Relapsed or refractory disease for transplant-ineligible patients
Dose
Palliative intent for patients with limited life expectancy: hypofractionated schedule of 8-30 Gy depending on surrounding dose-limiting structures, disease size, and patient performance status
Curative intent for patients with locoregionally confined disease: 45-55 Gy in 1.8-2 Gy/fraction; consider replanning midway into treatment, reduce treatment volume after 36 Gy, and adjust final dose depending on response
For bulky refractory disease, consider concurrent chemotherapy (eg, cisplatin-based chemotherapy as sensitizer) and RT to 39.6-40 Gy in 1.8-2 Gy/fraction
Volume
Palliative intent: limit to sites of relapse or refractory disease or causing symptoms requiring local palliation
Curative intent: consider more generous clinical target volume definition and inclusion of initial adjacent sites, if feasible
Scenario 5: Secondary CNS lymphoma: isolated brain parenchymal relapse
Dose
Complete response to CNS-directed chemotherapy: whole brain dose of 30 Gy in 1.5-2 Gy/fraction; in patients aged >60 y, consider whole brain dose of 23.4 Gy in 1.8 Gy/fraction to limit neurotoxicity
Partial response to CNS-directed chemotherapy: whole brain dose of 39.6-45 Gy in 1.8 Gy/fraction; in patients aged >60 y, consider whole brain dose of 23.4-30.6 Gy in 1.5-2 Gy/fraction, with sequential or integrated boost to gross residual disease to total dose of 39.6-45 Gy in 1.5-2.25 Gy/fraction
Volume
Whole brain; a lower whole brain dose with a boost to gross disease can be considered for patients aged >60 y

(continued on next page)

Table 2 (continued)

Scenario 6: Relapse/refractory primary brain lymphoma after CNS-directed chemotherapy

Dose

Whole brain dose of 36-45 Gy in 1.8-2 Gy/fraction depending on performance status and life expectancy

For patients aged >60 y with limited volume relapse, consider a whole brain dose 23.4-30.6 Gy in 1.5-2 Gy/fraction, with sequential or integrated boost to gross residual disease to total dose of 39.6-45 Gy in 1.5-2.25 Gy/fraction, with orbital dose of 36 Gy in 1.5-2 Gy/fraction if evidence of ocular involvement

Volume

Whole brain; a lower whole brain dose with a boost to gross disease can be considered for patients aged >60 y, with inclusion of bilateral orbits if evidence of ocular involvement

Scenario 7: Relapse/refractory primary mediastinal large B-cell lymphoma

Timing

Post-transplant RT (preferred) because of pneumonitis risk with pretransplant mediastinal RT

Pretransplant RT if refractory disease to salvage chemotherapy

Dose

Post-transplant RT: dose and volume recommendations same as those for relapsed DLBCL

Pretransplant for refractory disease: dose and volume recommendations same as those for refractory DLBCL; efforts should be made to limit MLD to <13.5 Gy and lung V5 to <55% but ultimately should not compromise dose to target volume

Volume/technique

Butterfly IMRT or VMAT, or proton beam therapy, with deep-inspiration breath hold to limit doses to lungs and heart and to the breasts in women

Abbreviations: BID = twice daily; CNS = central nervous system; DLBCL = diffuse large B-cell lymphoma; FDG = ¹⁸F-fluorodeoxyglucose; ILROG = International Lymphoma Radiation Oncology Group; IMRT = intensity modulated radiation therapy; ISRT = involved-site radiation therapy; MLD = mean lung dose; MSKCC = Memorial Sloan Kettering Cancer Center; PET/CT = positron emission tomography/computed tomography; RT = radiation therapy; VMAT = volumetric modulated arc therapy.

all with initial disease <5 cm and residual nodal masses <2 cm, suggests that RT is important even for patients with a complete anatomic response to salvage chemotherapy.

Recommendations

Timing

Previous studies of peritransplant RT included patients treated with pretransplant or post-transplant RT. A post-

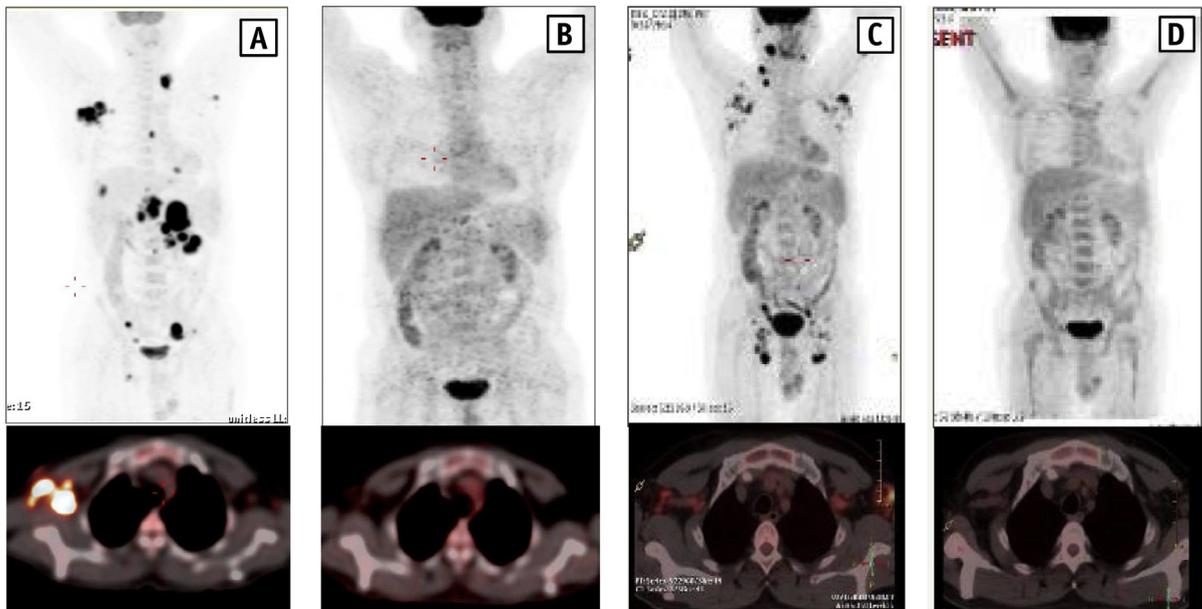


Fig. 1. Case example of relapsed diffuse large B-cell lymphoma (DLBCL) after primary chemotherapy, with a complete metabolic response to salvage chemotherapy. (A) Advanced-stage DLBCL, (B) complete metabolic response after 6 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone), (C) biopsy-proven relapsed disease on follow-up scan, and (D) Deauville 2 response after 2 cycles of R-ICE (rituximab, ifosfamide, etoposide, and carboplatin).

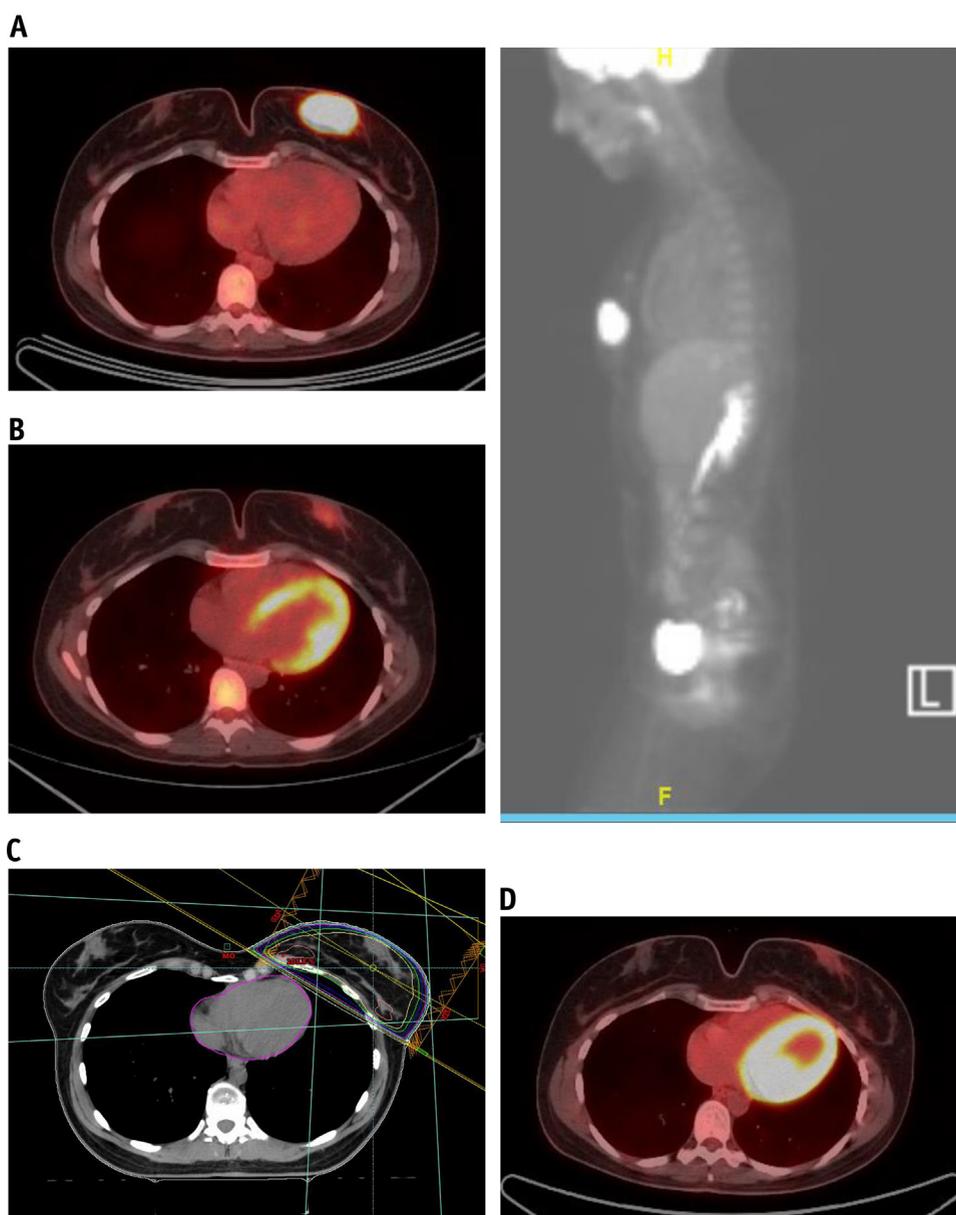


Fig. 2. Case example of relapsed diffuse large B-cell lymphoma (DLBCL) treated with post-transplant radiation therapy (RT). (A) A 32-year-old woman with a history of stage IV DLBCL after R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for 6 cycles; 18 months later, she was found to have biopsy-proven relapse localized to the left breast. (B) Restaging positron emission tomography/computed tomography (PET/CT) showing a Deauville 3 response after R-ICE for 2 cycles; the patient subsequently underwent high-dose therapy with autologous stem cell transplantation (HDT-ASCT). (C) Isodose distribution of post-transplant RT to the left breast to 30 Gy, using a tangential approach and deep-inspiration breath-hold technique. (D) Follow-up PET-CT scan 4 months after RT, showing a Deauville 2 response.

transplant RT approach for patients with a Deauville 1-3 response to salvage chemotherapy has a lower toxicity profile, potentially allows for a smaller RT volume in some cases, and is the preferred approach. Ideally, the RT should start within 4 to 12 weeks after transplantation, depending on the patient's recovery. Per institutional preference, pre-transplant RT is also a reasonable option because the MSKCC data (6) showed that in more recently treated patients, pretransplant accelerated RT (over 10 days) with

smaller fields and better supportive care is associated with limited morbidity.

Dose

In the context of a complete metabolic response to salvage chemotherapy and post-transplant RT, we recommend a dose of 30 to 36 Gy at 1.5 to 2 Gy/fraction. The dose recommendation is the same for the pretransplant RT setting. However, a hyperfractionated approach of 30 Gy at

1.5 Gy/fraction twice daily, such as in the MSKCC regimen, can be used. For patients with a history of RT, we recommend adherence to the recommended salvage RT doses as much as possible without exceeding the dose limits for the organs at risk. Highly conformal techniques, including intensity modulated RT and proton therapy, can be especially beneficial in the reirradiation setting.

Volume

For nodal relapses, we recommend limiting the treatment volume to the nodal sites of relapse. However, adjacent nodal disease that responded to first-line chemotherapy can be included in the clinical target volume, provided that its inclusion is not associated with significant toxicity. For extranodal relapses (Fig. 2), the target volumes should follow the involved-site RT principles from the International Lymphoma Radiation Oncology Group extranodal NHL guidelines (25).

Scenario 2: Relapsed or refractory disease after primary chemotherapy with overall reduction in FDG uptake but focus or foci of residual FDG avidity (Deauville 4-5) after salvage chemotherapy

A case example of scenario 2 is shown in Fig 3. A number of studies have shown that positive PET findings before transplantation are associated with significantly worse outcomes (13-18). In 1 study from the MSKCC, 129 patients with relapsed/refractory DLBCL (14), all deemed to have chemosensitive-disease based on the CT response to second-line chemotherapy, also underwent PET evaluations before HDT-ASCT. Patients with a Deauville response of 1-3 to salvage chemotherapy had superior PFS and OS rates of 77% and 86%, respectively, compared with patients achieving a Deauville 4 response (49% and 54%, respectively; $P < .001$).

Recommendations

Timing

Because of the inferior outcomes associated with residual FDG avidity immediately before transplant, we favor the administration of RT before transplantation in an attempt to achieve a complete metabolic response. The RT should start as soon as the patient has recovered from the last course of salvage chemotherapy, ideally within 4 weeks, and transplantation should occur within 4 weeks after RT completion. In addition, if it is anticipated that a significant amount of bone marrow will be included in the treatment volume (eg, pelvic disease), stem cell harvest should be completed before initiating RT to ensure adequate stem cell collection. Although our recommendation is for pretransplant RT for patients without a complete metabolic response to salvage chemotherapy, scenarios could occur in which these patients proceed directly to transplantation without RT and are then referred for post-transplant RT. The dose considerations in this setting are also included in the next section.

Dose

For pretransplant RT for patients with residual FDG avidity, we recommend a dose of 36 Gy in 1.8 to 2 Gy/fraction, with either a sequential or integrated boost to a final dose of 40 to 45 Gy in 1.8 to 2.2 Gy/fraction to the site of residual FDG-avid disease. In the post-transplant RT setting, if the post-transplant restaging PET-CT scan shows a complete metabolic response (Deauville 1-3), we recommend a dose of 36 Gy in 1.8 to 2 Gy/fraction. If the post-transplant restaging PET-CT scan shows residual FDG avidity, we recommend a dose of 36 Gy in 1.8 to 2 Gy/fraction, with either a sequential or an integrated boost to a final dose of 40 to 45 Gy in 1.8 to 2.2 Gy/fraction to the sites of residual FDG-avid disease.

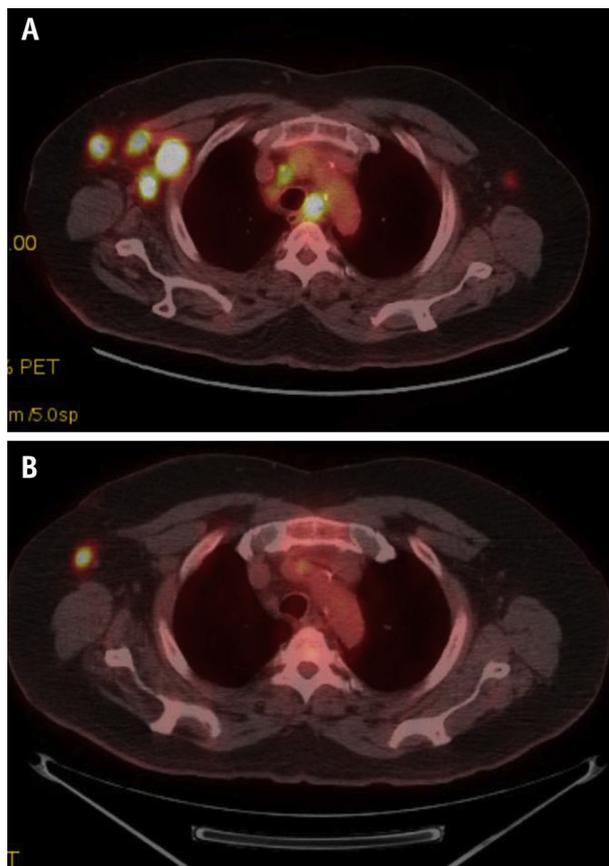


Fig. 3. Case example of relapsed diffuse large B-cell lymphoma (DLBCL), responsive to salvage chemotherapy but with residual ^{18}F -fluorodeoxyglucose (FDG)-avid focus. (A) Relapsed DLBCL with mediastinal and right axillary involvement, and (B) resolution of mediastinal disease and significant reduction of right axillary disease with a residual FDG-avid focus after R-ICE (rituximab, ifosfamide, etoposide, and carboplatin) for 2 cycles.

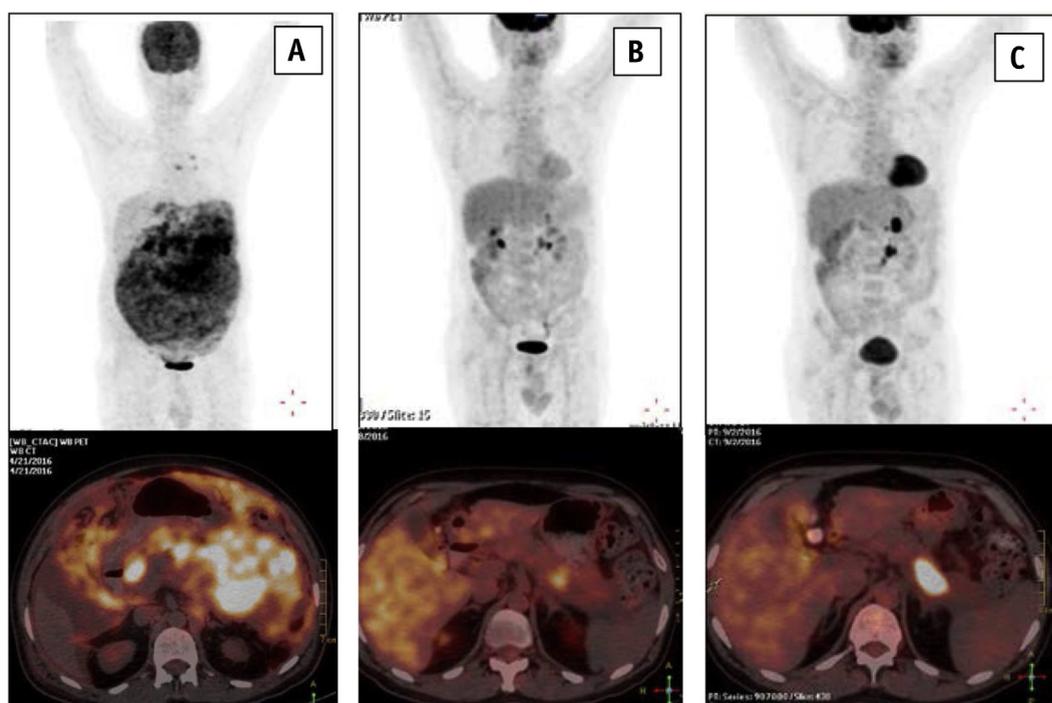


Fig. 4. Case example of chemotherapy-refractory lymphoma. (A) diffuse large B-cell lymphoma (DLBCL) with extensive abdominal involvement, (B) interim positron emission tomography/computed tomography (PET/CT) scan after R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for 4 cycles, with a Deauville 4 response, and (C) PET/CT scan after R-CHOP for 6 cycles, showing progression; Deauville 5.

Volume

The volume should be the same as that for Scenario 1.

Scenario 3: Localized refractory disease to primary or salvage chemotherapy

A case example of scenario 3 is shown in Fig 4. The prognosis of patients with chemotherapy-refractory disease is poor. However, for patients with refractory disease ie, localized, RT can be an effective salvage modality, providing an opportunity to achieve remission and serving as a bridge to HDT-ASCT with curative intent for those who are potential transplantation candidates.

Recommendations

Timing

For localized chemotherapy-refractory disease in patients who are potential transplant candidates, RT should be administered before transplantation in an attempt to achieve a minimal disease state before the transplant (Fig. 5). The RT should start as soon as the patient has recovered from the last course of salvage chemotherapy, ideally within 4 weeks, with transplantation within 4 weeks after RT completion. In addition, if it is anticipated that a

significant amount of bone marrow will be included in the treatment volume (eg, pelvic disease), stem cell harvest should be completed before initiating RT to optimize adequate stem cell collection.

Dose

Chemotherapy-refractory disease also tends to be less responsive to RT and therefore a higher dose of radiation will be needed (26-29). For pretransplant salvage RT for chemotherapy-refractory disease, we recommend a dose of 40 to 50 Gy at 1.8 to 2 Gy/fraction, depending on the volume, location, and surrounding dose-limiting structures. If evidence is found of rapid disease growth during chemotherapy, a hyperfractionated approach can be considered, at 1.3 to 1.5 Gy twice daily to a total dose of 35 to 40 Gy (28).

Volume

The volume should be the same as that for Scenario 1.

Scenario 4: Relapsed or refractory disease for transplant-ineligible patients

For patients with recurrent or refractory NHL who are not transplant candidates, RT can provide effective palliation and, in some instances, might have a potentially curative

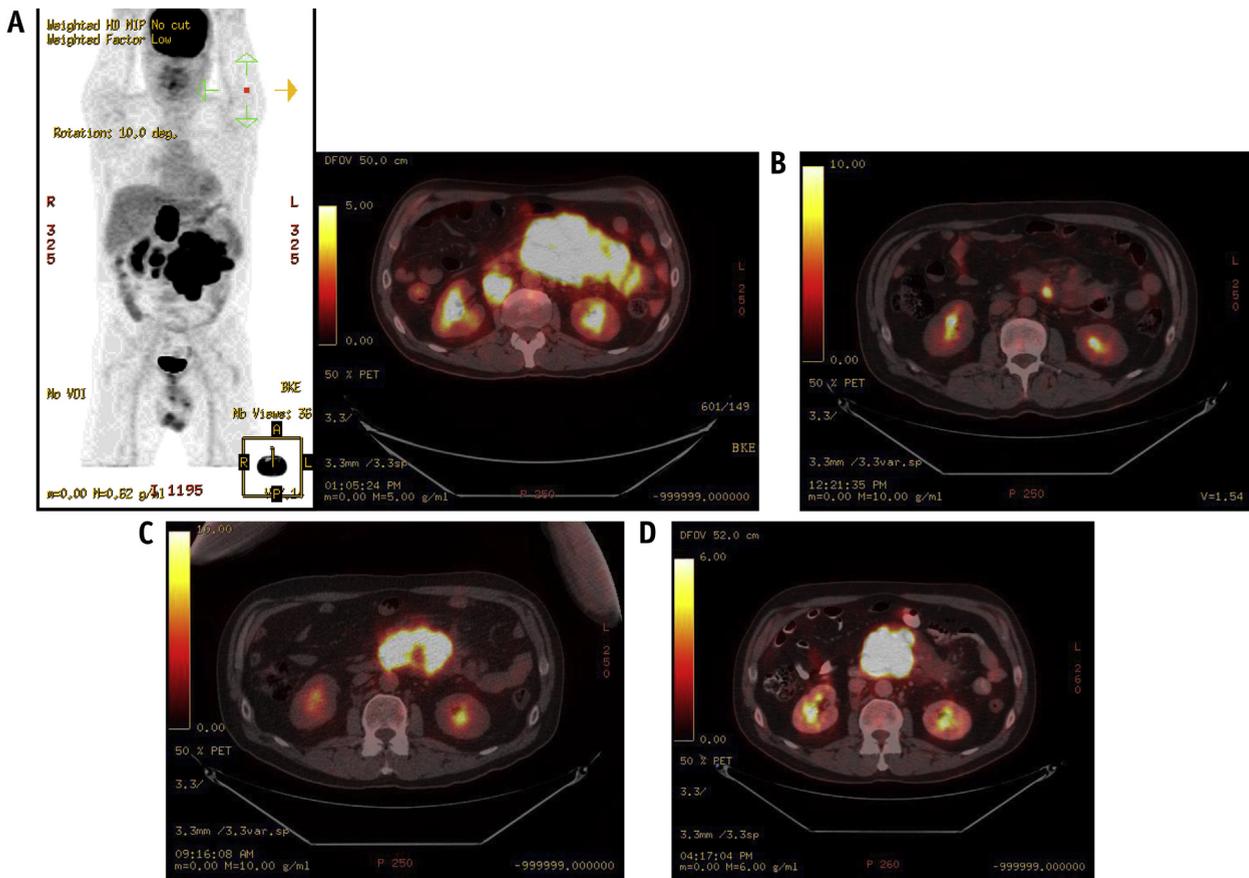


Fig. 5. Case example of refractory transformed lymphoma treated with pretransplant radiation therapy (RT). (A) A 51-year-old man with a history of follicular lymphoma with transformed lymphoma involving the mesentery. (B) Positron emission tomography/computed tomography (PET/CT) scan showing a Deauville 5 response after R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for 6 cycles. (C) Repeat PET/CT scan after R-ICE (rituximab, ifosfamide, etoposide, and carboplatin) for 2 cycles showed progressive disease. (D) Repeat PET/CT scan after R-DHAP (rituximab, dexamethasone, high-dose cytarabine, cisplatin) for 2 cycles showed persistent disease; the patient then received hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) for 2 cycles and salvage RT to 45 Gy. (E) Isodose distribution of salvage RT to 45 Gy. (F) Dose-volume histograms of RT plan. (G) PET/CT scan after RT showing an excellent response; the patient subsequently underwent high-dose therapy with autologous stem cell transplantation and remained in remission.

role. Examples of indications for palliative RT include lymphoma involvement causing pain, neurologic compromise, obstruction, and bleeding. In patients with bulky, chemotherapy-refractory disease, concurrent chemotherapy and RT can be considered. This approach has been shown to improve clinical outcomes, especially local control, in numerous epithelial malignancies. With the exception of extranodal nasal-type natural killer/T-cell lymphoma, this strategy has not been systemically explored in hematologic malignancies. A small phase 2 study evaluated a split course of RT (40 Gy with a 2- to 3-week break after 20 Gy) with concurrent chemotherapy, primarily cisplatin and etoposide, for patients with bulky refractory lymphoma (27). At 1 year, local control was ~50%. Ideally, the agents would have demonstrated single-agent activity against the particular lymphoma and be a known radiosensitizer with a known safety profile in similar settings.

In patients with locoregionally confined FDG-avid disease after primary chemotherapy, RT can potentially be curative. In a study from British Columbia (30), of the 60 patients with FDG-avid disease after R-CHOP who had received RT to doses of 30 to 45 Gy, only 10 developed a relapse (6 of 10 in-field), yielding a 4-year time-to-progression of 81%. However, the results of that study are only available in abstract form.

Recommendations

Dose

In patients with a limited life expectancy, a hypofractionated schedule of total doses of 8 to 30 Gy, depending on the surrounding dose-limiting structures, disease size, and patient performance status, is recommended as palliation. For patients receiving concurrent chemotherapy and RT for bulky refractory disease, we recommend an RT dose of 39.6 to 40 Gy in 1.8 to

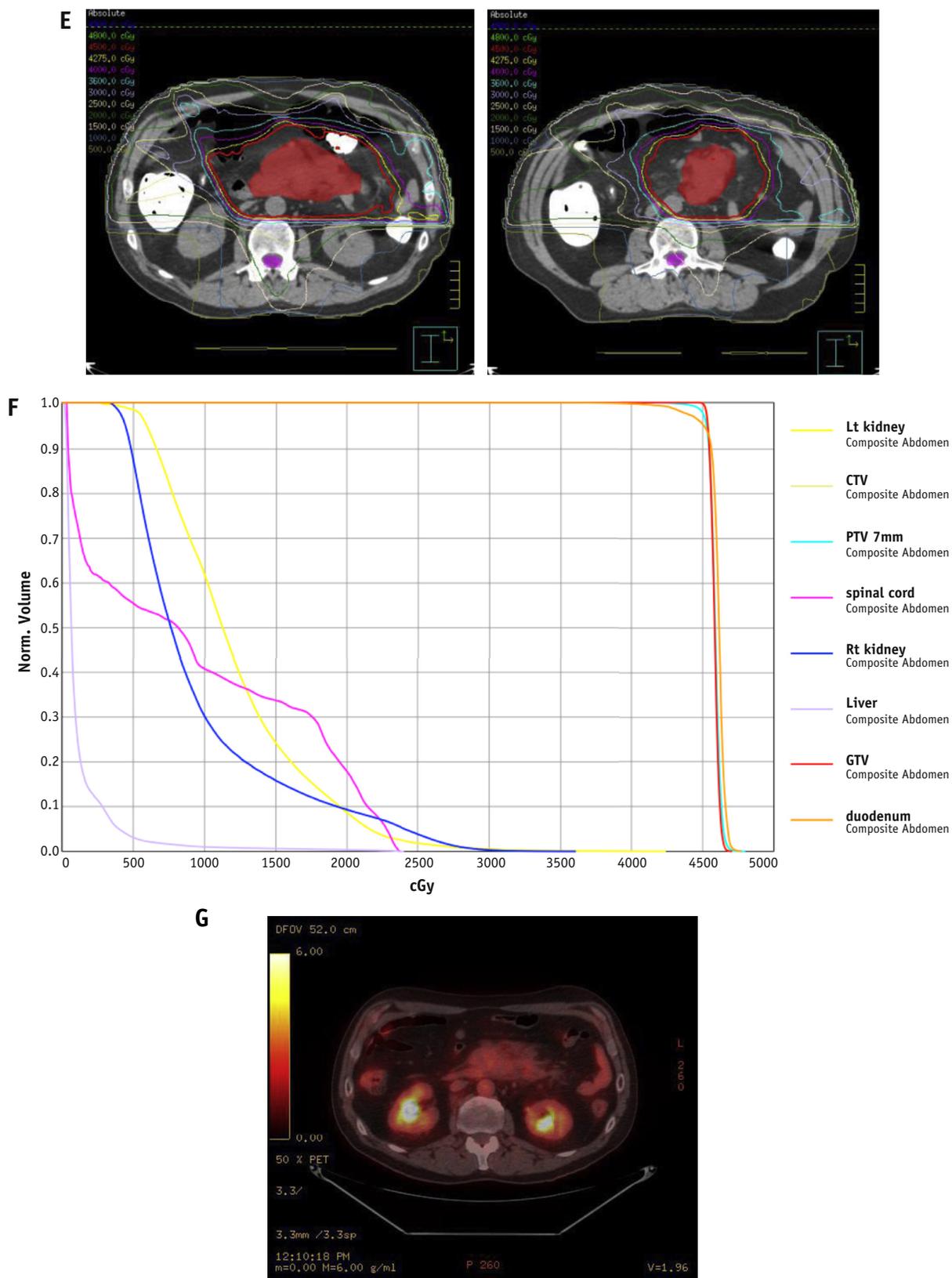


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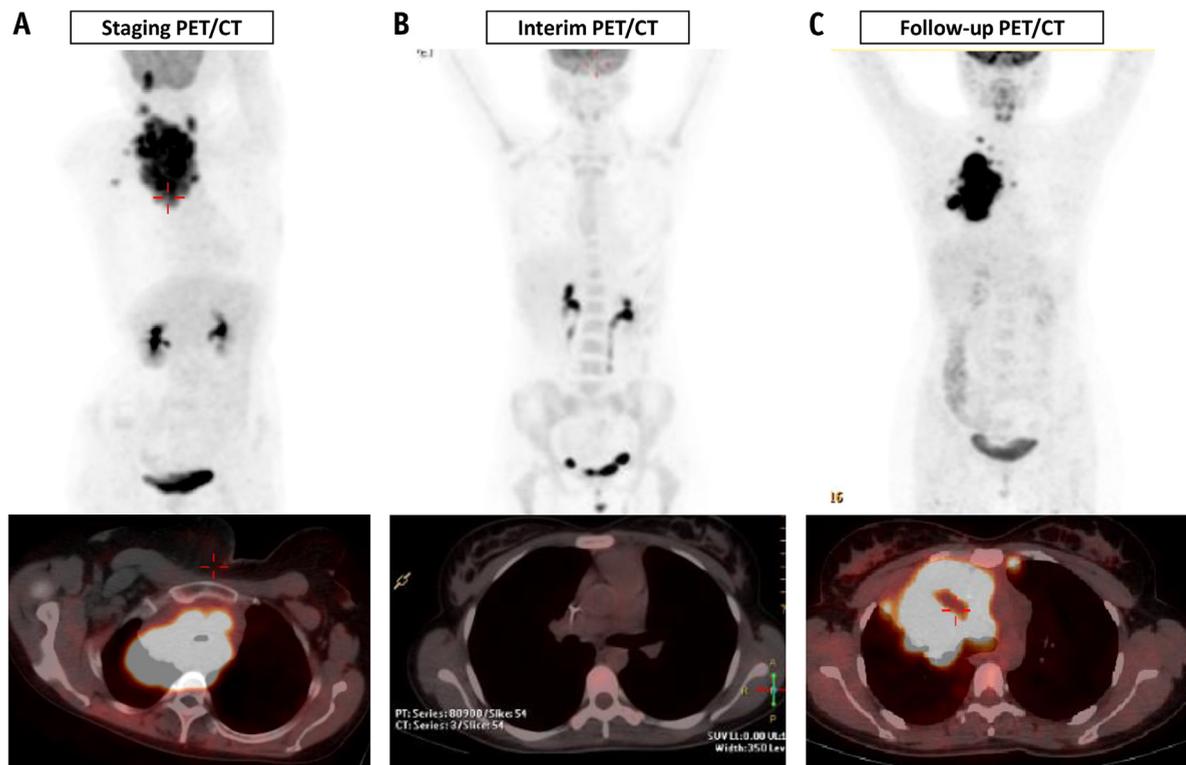


Fig. 6. Case example of relapsed primary mediastinal large B-cell lymphoma (PMBL) after DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab). (A) Staging positron emission tomography/computed tomography (PET/CT) scan of PMBL, (B) restaging PET/CT scan showing complete metabolic response to 6 cycles of DA-EPOCH-R, and (C) follow-up PET/CT scan 4 months after treatment showing relapse in the mediastinum.

2 Gy/fraction. In patients with locoregionally confined relapsed or refractory disease, RT with potentially curative intent should be considered. In such situations, a higher dose of 45 to 55 Gy in 1.8 to 2 Gy/fraction is recommended. It might be of benefit to perform reimaging with PET-CT approximately midway into treatment to assess the response, perform replanning to reduce the treatment volume after 36 Gy, and adjust the final dose, depending on the response.

Volume

For RT with palliative intent, we recommend limiting treatment volumes to the sites of relapse or refractory disease or to sites that are causing symptoms requiring palliation. For RT with curative intent, we recommend a more generous clinical target volume definition and the inclusion of initial sites of involvement if they are in close proximity and the inclusion will not cause excessive toxicity.

Scenario 5: Secondary central nervous system lymphoma: isolated brain parenchymal relapse

For patients with systemic lymphoma, central nervous system (CNS) relapses can occur in $\leq 5\%$ of cases and can involve the brain parenchyma, spinal cord, and nerve roots and/or can have ocular involvement (31, 32).

In a small proportion of patients with an isolated brain parenchymal relapse without evidence of systemic lymphoma, the possibility exists for cure with aggressive treatment, as shown in the study by the International Primary CNS Lymphoma Collaborative Group (32). In their study, 113 patients were evaluated who had systemic NHL with a complete response to the initial treatment and who then developed an isolated relapse in the brain. For salvage therapy, 46% received chemotherapy (mostly systemic methotrexate-based) only, 23% received both chemotherapy (mostly systemic methotrexate-based) and whole brain RT and 30% received whole brain RT only. The median OS was 1.6 years, with 23% of patients surviving ≥ 3 years, 16% surviving ≥ 4 years, and 11% surviving ≥ 5 years, suggesting that long-term survival can be achieved in a subset of patients. The best predictor for the interval to progression was treatment with methotrexate and whole brain RT (hazard ratio, 0.45; $P = .013$).

Recommendations

In patients with systemic lymphoma with isolated brain relapse, we recommend starting with CNS-directed chemotherapy, followed by whole brain RT. In the International Primary CNS Lymphoma Collaborative Group study (32), the median whole brain RT dose was 30 Gy, although the study was not designed to evaluate the optimal RT dose. If a

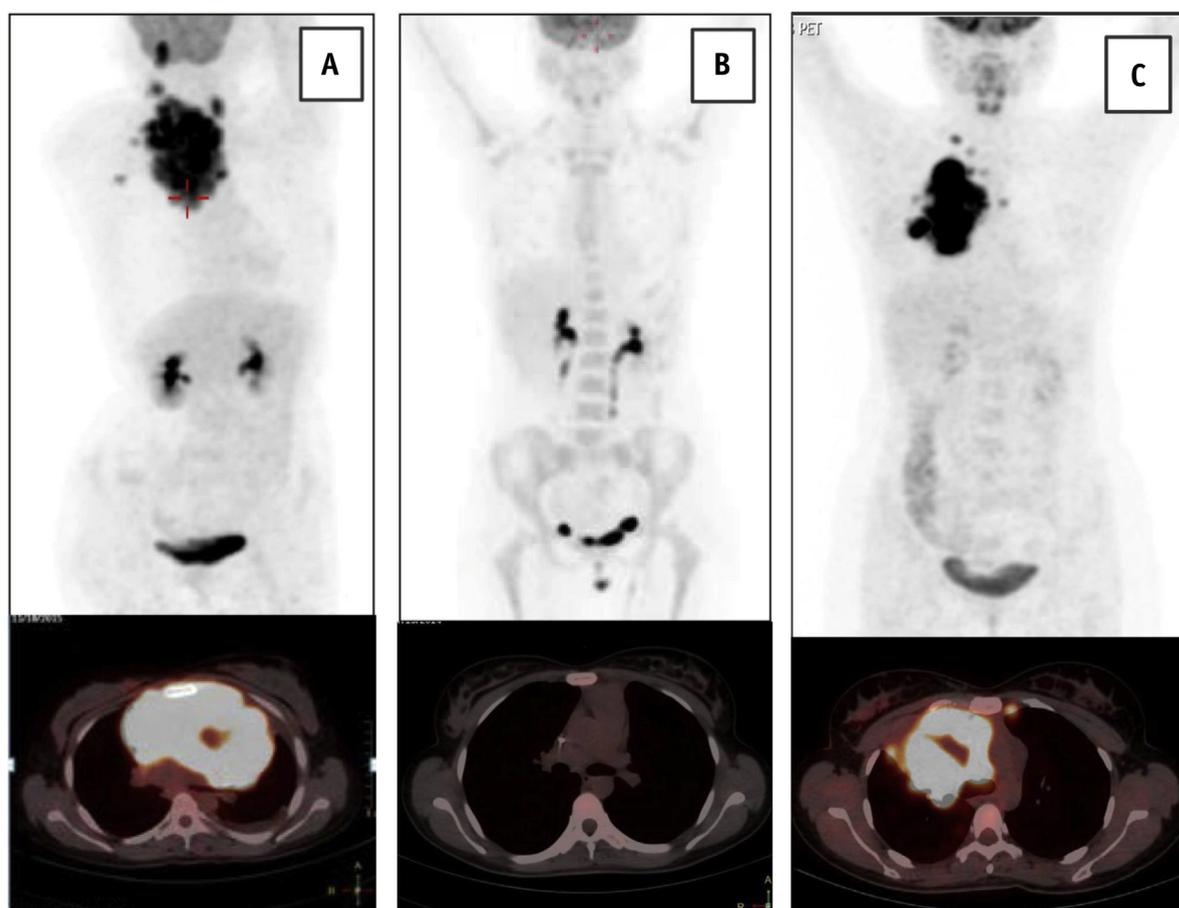


Fig. 7. Case example of refractory primary mediastinal large B-cell lymphoma (PMBL). (A) Staging positron emission tomography/computed tomography (PET/CT) of PMBL, (B) interim PET/CT scan after 4 cycles of DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) showing a Deauville 4 response, (C) restaging PET/CT scan at the end of 6 cycles of DA-EPOCH-R showing progressive disease in the mediastinum; Deauville 5 response.

complete response (as assessed by magnetic resonance imaging) to chemotherapy is achieved, we recommend a whole brain dose of 30 Gy in 1.5 to 2 Gy/fraction. A lower dose of 23.4 Gy in 1.8 Gy/fraction in the setting of a complete response can be considered, extrapolating data from a combined modality therapy approach for primary CNS lymphoma from the MSKCC (33), especially in patients aged >60 years for whom neurotoxicity is a concern. However, the lower dose should be used judiciously, because its efficacy has only been shown in primary disease. Also, patients received further consolidative chemotherapy in the MSKCC experience. If the response is less than complete, a whole brain RT dose of 39.6 to 45 Gy in 1.8 Gy/fraction is recommended. Evidence favoring a boost radiation dose is lacking and thus not generally recommended. Supporting this is data from the historical Radiation Therapy Oncology Group (RTOG) 8315 trial of primary CNS lymphoma that included a whole brain RT dose of 40 Gy, followed by a 20-Gy boost (34), for cases with a continued high risk of in-field recurrences. However, the role of a boost in the era of magnetic resonance imaging and modern, effective CNS-directed

therapy remains undefined. In patients aged >60 years with relapsed/refractory disease after CNS-directed chemotherapy and in whom neurotoxicity is a significant concern, a whole brain RT dose of 23.4 to 30.6 Gy in 1.5 to 2 Gy/fraction, with a sequential or an integrated boost to gross disease to 39.6 to 45 Gy in 1.5 to 2.25 Gy/fraction, is a reasonable alternative. For patients with ocular involvement, we recommend inclusion of the bilateral orbits to a dose of 23.4 to 30.6 Gy if a complete response has been achieved with CNS-directed chemotherapy; otherwise, a dose of 36 Gy is appropriate.

Scenario 6: Relapsed/refractory primary or secondary CNS lymphoma after CNS-directed chemotherapy

In patients with primary or secondary CNS lymphoma who either develop a relapse after, or who are refractory to, CNS-directed chemotherapy, salvage RT can provide effective palliation and in some cases long-term disease control (35-37). In patients with relapsed or refractory CNS

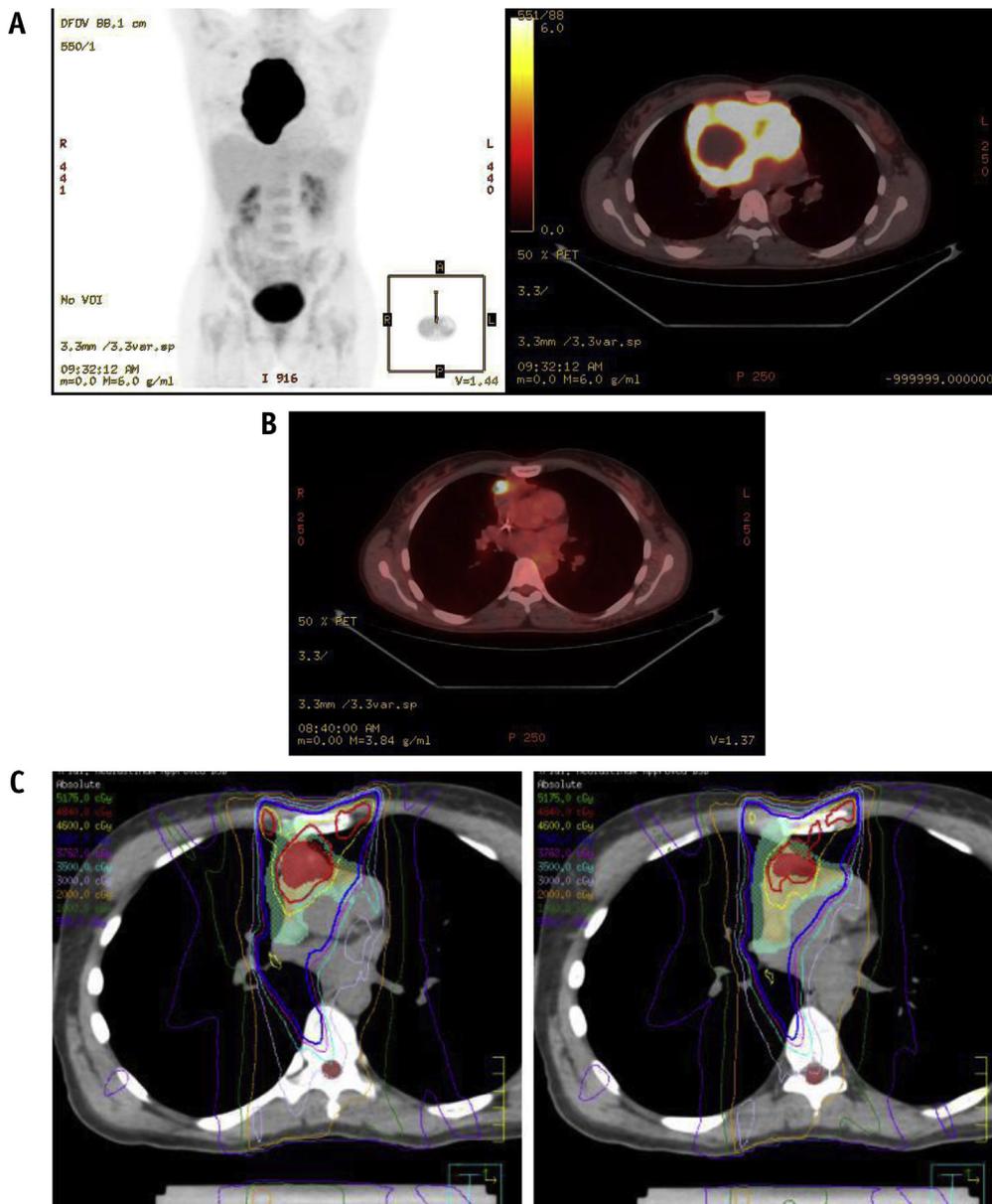


Fig. 8. Case example of refractory primary mediastinal large B-cell lymphoma (PMBL) treated with pretransplant radiation therapy (RT). (A) A 44-year-old woman with PMBL treated with DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) for 6 cycles with a focus of persistent ¹⁸F-fluorodeoxyglucose (FDG)-avid disease (Deauville 5 response). (B) Restaging positron emission tomography/computed tomography (PET/CT) scan after 2 cycles of R-DHAP (rituximab, dexamethasone, high-dose cytarabine, cisplatin) showed no response. (C) Isodose distribution of salvage RT with butterfly intensity modulated RT technique with dose painting of 39.6 Gy in 1.8 Gy/fraction to initial disease extent and 48.4 Gy in 2.2 Gy/fraction to area of FDG-avid disease. (D) Dose-volume histograms of RT plan, with a lung V5 of 33.5%.

lymphoma and good performance status, HDT-ASCT has been used as salvage, although these programs have not typically included the use of RT (38-41).

Several studies have explored the role of salvage whole brain RT for patients with primary or secondary CNS lymphoma who either developed a relapse after or had refractory disease to CNS-directed chemotherapy (35-37). The median RT dose in these studies ranged from 36 to 40 Gy. The median OS from the time of salvage whole

brain RT ranged from 10.9 to 16 months, with a small subset of patients surviving >5 years.

Recommendations

In patients with relapsed or refractory disease after CNS-directed chemotherapy, we recommend considering whole brain RT to a dose of 36 to 45 Gy in 1.8 to 2 Gy/fraction, depending on the patient’s performance status and estimated life expectancy. In patients aged >60 years with

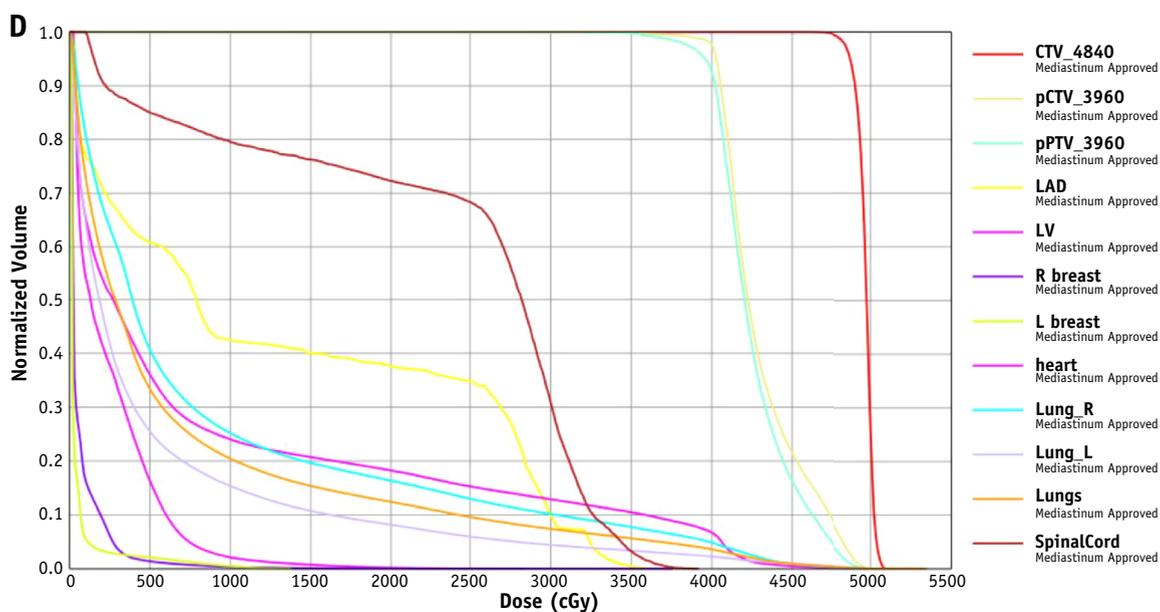


Fig. 8. (continued).

relapsed/refractory disease after CNS-directed chemotherapy and for whom neurotoxicity is a significant concern, a whole brain RT dose to 23.4 to 30.6 Gy in 1.5 to 1.8 Gy/fraction, with a sequential or an integrated boost to gross disease to 39.6 to 45 Gy in 1.5 to 2.25 Gy/fraction, can be considered. For patients with evidence of ocular involvement, we recommend inclusion of the bilateral orbits to a dose of 36 Gy.

Scenario 7: Relapsed/refractory primary mediastinal large B-cell lymphoma

For patients with primary mediastinal large B-cell lymphoma (PMBL), treatment with rituximab-based chemotherapy results in event-free survival rates ranging from 70% to 93% (42) (Figs. 6 and 7). Relapsed or primary refractory PMBL is associated with a poor prognosis (43), with an overall response rate to salvage chemotherapy of only 25% and a 2-year OS rate of only 15%. However, for those who were able to undergo HDT-ASCT, the 2-year PFS and OS rates were 57% and 67%, respectively (43). In a study from the MD Anderson Cancer Center on 97 patients with PMBL treated with R-CHOP, R-Hypercyclophosphamide, vincristine, doxorubicin, dexamethasone (CVAD) or dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab (DA-EPOCH-R) with or without RT (44), 9 (10%) experienced progressive ($n = 8$) or relapsed ($n = 1$) disease. All the patients who received RT as part of their salvage program that included ASCT remained in remission.

Recommendations

Our recommendations on the indications for RT as part of salvage for relapsed/refractory PMBL are similar to those

for other aggressive NHLs as outlined in previous scenarios, with the exception of the definition of refractory disease. In the phase 2 trial of DA-EPOCH-R for PMBL, 18 patients had residual FDG-PET avidity greater than mediastinal blood pool levels at the end of chemotherapy (45). Only 3 of the 18 patients developed a relapse, for a positive predictive value of only 17%. In the IELSG-26 study of 125 patients with PMBL (46), 115 patients had evaluable PET-CT scans available 3 to 4 weeks after immunochemotherapy. Among the 24 patients with a Deauville score of 4 after immunochemotherapy, 21 subsequently underwent RT, and 19 of the 21 patients achieved long-term complete remission. This suggests that of patients with PMBL and a Deauville score of 4 after immunochemotherapy, who then receive consolidative RT, most can be cured.

The timing, RT dose, and volume for patients with biopsy-proven refractory and relapsed PMBL should otherwise follow the same principles as those for other aggressive NHLs. Post-transplant RT is preferred because of the pneumonitis risk when RT precedes HDT (21, 22). When pre-transplant RT is necessary owing to refractoriness to salvage chemotherapy, efforts should be made to achieve a mean lung dose of <13.5 Gy and lung V5 to $<55\%$ but, ultimately, should not compromise the target dose (Fig. 8) (21). Butterfly intensity modulated RT or volumetric modulated arc therapy and proton beam therapy (47), along with deep inspiration breath-hold, are encouraged to limit the doses to the lungs and heart and to the breasts in women (48-50).

Effect of New Therapies

The use of immunotherapy for lymphoma, including immune checkpoint inhibitors, adoptive cell therapy, new monoclonal antibodies, therapeutic vaccines, and cytokines

and novel targeted agents is rapidly evolving and is under active investigation through multiple ongoing studies (51). The response assessment can be challenging owing to the tumor flare associated with immunomodulatory therapy (52). In addition, long-term disease control with these newer agents is currently unknown. RT, which has a known track record of durable lymphoma control, should therefore be incorporated whenever indicated and feasible. At present, data are lacking on how best to use RT in conjunction with these novel agents. Patients are sometimes referred for RT while awaiting the opening of a new clinical trial or the availability of an opening in a clinical trial of the novel agents. In this setting, especially for patients with locally limited disease, it is important not to compromise on the RT dose and volume. Also, definitive RT should be incorporated whenever possible. In addition, until more data are available, we recommend avoiding concurrent administration of RT. Pneumonitis is an uncommon, but potentially fatal, toxicity of anti-programmed death-1/programmed death ligand 1 monoclonal antibodies (53). Brentuximab vedotin, used in the salvage setting for CD30⁺ aggressive NHL, has also been shown to result in serious pulmonary toxicity in Hodgkin lymphoma, especially when combined with other pulmonary toxic therapy (54, 55). In addition, targeted agents such as idelalisib and ibrutinib have been associated with enterotoxicity and hepatotoxicity (56, 57). We therefore recommend, as much as possible, adherence to the metrics for the organs at risks, including lung, liver, and bowel metrics, when RT to relevant sites is used in conjunction with these agents, because of the unknown added toxicity and interactions with RT. It is necessary to accumulate data on the use of RT in the context of these novel agents for a better understanding of the response rates, toxicities, and long-term efficacy.

Conclusions

Relapsed/refractory DLBCL is associated with a poor prognosis, and only a few patients will achieve long-term cure. On the basis of the limited available data, peritransplant RT improves local control and outcomes in patients with chemosensitive disease and provides an opportunity for curative treatment in a subset of patients with localized chemorefractory disease. For transplant-ineligible patients, RT can provide effective local palliation. On rare occasions, patients with localized relapsed/refractory disease can be offered RT with curative intent. Higher doses of 40 to 50 Gy, hyperfractionation or a radiation sensitizer might be needed for chemorefractory disease. As novel agents are increasingly being evaluated and adopted for the treatment of relapsed/refractory DLBCL, additional data on RT timing and dose fractionation and updated metrics on dose tolerances for organs at risk are needed to improve the treatment outcomes for these patients.

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